VOLUME 95 • APRIL 1958 • NUMBER 4

A.M.A. JOURNAL OF

DISEASES OF CHILDREN

Poliovirus Neutralizing Antibody Levels in Pediatricians and Preclinical Faculty Members
Paul F. Wehrle, Gerson Aronovitz, Robert Zechnich, and Paul Parkman

Vaccination Against Poliomyelitis
Lewis L. Coriell

Failure of Penicillin and Sulfonamide to Prevent Beta-Hemolytic Streptococcal Infections
Burtis B. Breese and F. A. Disney

Addison's Disease in Three Six-Year-Old Boys
Bernard Mathis Malloy and Calvin W. Woodruff

Speech- and Language-Handicapped Children
Isaac W. Karlin

Renal Vein Thrombosis
Herbert J. Kaufmann

Ataxia, Telangiectasia, and Sinopulmonary Infections
Willard R. Centerwall and Melba M. Miller

Promethazine Suppositories for Management of Nausea and Vomiting in Children
Thomas E. Cone Jr.

The Urinary Excretion of Poster-Silber Chromogens by Premature Infants
Robert L. Cranny and Caroline L. Cranny

Female Pseudohermaphroditism with Penile Urethra
Lorin E. Ainger, Gerardo C. Zapata. Robert S. Ely, and Vincent C. Kelley

The Coil-Spring Sign and Intramural Hematoma of the Proximal Small Intestine
Kenneth F. Swaiman, Jill F. Root, and Richard B. Raile

Acute Tubular Necrosis in Infancy and Childhood
Geoffrey C. Robinson and Lei Ching Wong

Abstracts from Current Literature

News and Comment

Books

AMERICAN MEDICAL ASSOCIATION PUBLICATION

In Asthma

MEDIHALER®

automatic measured-dose aerosol medication

For Ample Air Right Now!

NOTHING IS QUICKER • NOTHING IS MORE EFFECTIVE

Medihaler-EPI®

For quick relief of bronchospasm of any origin. More rapid than injected epinephrine in acute allergic attacks.

Epinephrine bitartrate, 7.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each measured dose 0.15 mg. actual epinephrine.

Medihaler-ISO®

Unsurpassed for rapid relief of symptoms of asthma and emphysema.

Isoproterenol sulfate, 2.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each measured dose 0.06 mg. actual isoproterenol.

Prescribe Medihaler medication with Oral Adapter on first prescription. Refills available without Oral Adapter.

Medihaler-Phen®

Automatic NASAL aerosol nebulization provides prompt, effective, prolonged, and nonirritating decongestion in head colds, allergic rhinitis, sinusitis, and nasopharyngitis. Vasoconstrictive, decongestive, anti-inflammatory, antibacterial. Combines actions of phenylephrine, phenylpropanolamine, neomycin, and hydrocortisone.

FOR KIDDIES TOO

Notably well tolerated and effective for children. Nonbreakable, spillproof.

Riker LOS ANGELES

TABLE OF CONTENTS

VOLUME 95 APRIL 1958 NUMBER 4

ORIGINAL ARTICLES

PAGE

Poliovirus Neutralizing Antibody Levels in Pediatricians and Preclinical Faculty Members
Paul F. Wehrle, M.D.; Gerson Aronovitz, M.D.; Robert Zechnich, M.D., and Paul Parkman, M.D., Syracuse, N. Y. 341

Vaccination Against Poliomyelitis
Lewis L. Coriell, M.D., Camden, N. J. 349

Failure of Penicillin and Sulfonamide to Prevent Beta-Hemolytic Streptococcal Infections
Burtis B. Breese, M.D., and F. A. Disney, M.D., Rochester, N. Y. 359

Addison's Disease in Three Six-Year-Old Boys
Bernard Mathis Malloy, M.D., and Calvin W. Woodruff, M.D., Nashville, Tenn. 364

Speech- and Language-Handicapped Children
Isaac W. Karlin, M.D., Brooklyn 370

Renal Vein Thrombosis
Herbert J. Kaufmann, M.D., Boston 377

Ataxia, Telangiectasia, and Sinopulmonary Infections
Willard R. Centerwall, M.D., and Melba M. Miller, Ed.D., Los Angeles. 385

Promethazine Suppositories for Management of Nausea and Vomiting in Children
Capt. Thomas E. Cone Jr. (MC), U. S. N. 397

The Urinary Excretion of Poster-Silber Chromogens by Premature Infants
Robert L. Cranny, M.D., and Caroline L. Cranny, M.T., Salt Lake City. 401

CASE REPORTS

Female Pseudohermaphroditism with Penile Urethra
Lorin E. Ainger, M.D.; Gerardo C. Zapata, M.D.; Robert S. Ely, M.D., and Vincent C. Kelley, M.D., Ph.D., Salt Lake City 410

The Coil-Spring Sign and Intramural Hematoma of the Proximal Small Intestine
Kenneth F. Swaiman, M.D.; Jill F. Root, M.D., and Richard B. Rude, M.D., Minneapolis 413

PROGRESS IN PEDIATRICS

Acute Tubular Necrosis in Infancy and Childhood
Geoffrey C. Robinson, M.D., F. R. C. P. (C), and Lei Ching Wong, M.D., Vancouver, B. C., Canada 417

REGULAR DEPARTMENTS

Abstracts from Current Literature 434

News and Comment 449

Books:

Books Received 452

Book Reviews 452

A. M. A.
Journal of Diseases of Children

VOLUME 95 APRIL 1958 NUMBER 4

COPYRIGHT, 1958, BY THE AMERICAN MEDICAL ASSOCIATION

EDITORIAL BOARD

RICHARD L. DAY, Chief Editor
State University of New York College of Medicine, Downstate Medical Center
450 Clarkson Ave., Brooklyn 3

ROBERT A. ALDRICH, Seattle
RICHARD L. DAY, Brooklyn
ROGER L. J. KENNEDY, Rochester, Minn.
ROBERT B. LAWSON, Miami, Fla.
FRANCIS SCOTT SMYTH, San Francisco
A. A. WEECH, Cincinnati
WARREN E. WHEELER, Columbus, Ohio
JAMES L. WILSON, Ann Arbor, Mich.
WOLF W. ZUELZER, Detroit

ASSOCIATE EDITORS

SYDNEY S. GELLIS, Boston
ROBERT A. GOOD, Minneapolis
ROBERT JACKSON, Columbia, Mo.
VINCENT C. KELLEY, Salt Lake City
C. HENRY KEMPE, Denver
STUART S. STEVENSON, Pittsburgh
HENRY WORK, Los Angeles

AUSTIN SMITH, Editor, A. M. A. Scientific Publications
GILBERT S. COOPER, Managing Editor, Specialty Journals

SUBSCRIPTION RATES

Price per annum in advance, including postage: Domestic, $12.00. Canadian, $12.50 Foreign, $13.50. Price to students, interns, and residents, $7.00 in U. S. & possessions.

Single copies of this and previous calendar year, $1.25.

Back issues older than two years are available through Walter J. Johnson, Inc., 111 Fifth Avenue, New York 3. Future reprints of back issues will be available through Johnson Reprint Corporation, 111 Fifth Avenue, New York 3.

Checks, money orders, and drafts should be made payable to the American Medical Association, 535 North Dearborn Street, Chicago 10.

AMERICAN MEDICAL ASSOCIATION Publication

Published monthly by the AMERICAN MEDICAL ASSOCIATION. Editorial and Circulation Offices: 535 North Dearborn Street, Chicago 10, Illinois. Publication Office: Thompson Lane, Box 539, Nashville 1, Tennessee. Change of Address: Notice to the circulation office should state whether or not change is permanent and should include the old address. Six weeks' notice is required to effect a change of address. Second-class mail privileges authorized at Nashville, Tenn., Aug. 6, 1956.

NOW

antiemetic and full-range tranquilizer benefits extended to all age groups particularly children

Trilafon® Syrup

perphenazine 2 mg./tsp.

PRESCRIBE IT IN CHILDREN FOR

- nausea and vomiting
- behavioral problems
- mild, moderate and severe emotional and mental disorders

PRESCRIBE IT IN ADULTS FOR

- elderly patients who prefer liquid medication

PRESCRIBE IT BECAUSE

- behavioral and antiemetic potency are unexcelled
- mental acuity is usually unimpaired
- significant hypotension is absent
- agranulocytosis has not been reported

For dosage in children and adults, precautions and contraindications, consult Schering literature.

Packaging: TRILAFON Syrup, 2 mg. in each teaspoon (5 cc.), 4 oz. bottle.

outmoding older concepts

Schering

SCHERING CORPORATION • BLOOMFIELD, NEW JERSEY

TR-J-1530

Instructions to Contributors

Articles, book reviews, and other materials for publication should be addressed to the Chief Editor. Articles are accepted for publication on condition that they are contributed solely to this journal.

An original typescript of an article, with one carbon copy, should be provided; it must be double or triple spaced on one side of a standard size page, with at least a 1-inch margin at each edge. Another carbon copy should be retained by the author.

The main title of an article may not contain more than eighty characters and spaces; a subtitle may be of any length.

The author's name should be accompanied by the highest earned academic or medical degree which he holds. If academic connections are given for one author of an article, such connections must be given for all other authors of the article who have such connections.

If it is necessary to publish a recognizable photograph of a person, the author should notify the publisher that permission to publish has been obtained from the subject himself if an adult, or from the parents or guardian if a child. An illustration that has been published in another publication should be accompanied by a statement that permission for reproduction has been obtained from the author and the original publisher.

Oversized original illustrations should be photographed and a print on glossy paper submitted. Prints of a bluish tinge should be avoided. Large photomicrograph prints will be reduced in scale unless portions to be cropped are indicated by the author. The author should submit duplicate prints of roentgenograms and photomicrographs with the essential parts that are to be emphasized circled, as a guide to the photoengraver.

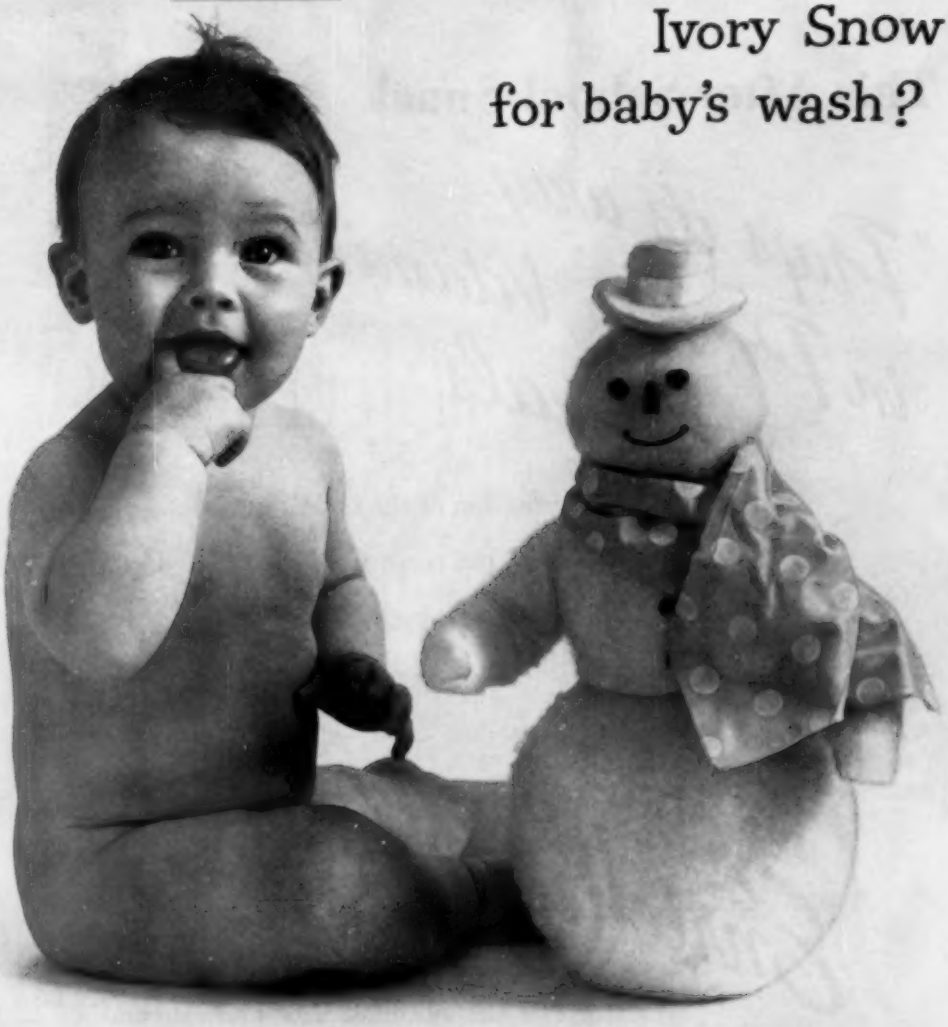
Charts and drawings should be in black ink on hard, white paper. Lettering should be large enough, uniform, and sharp enough to permit necessary reduction. Glossy prints of x-rays are requested. Paper clips should not be used on prints, since their mark shows in reproduction, as does writing on the back of prints with hard lead pencil or stiff pen. Labels should be prepared and pasted to the back of each illustration showing its number, the author's name, and an abbreviated title of the article, and plainly indicating the top. Charts and illustrations must have descriptive legends, grouped on a separate sheet. Tables must have captions. ILLUSTRATIONS SHOULD BE UNMOUNTED.

References to the literature should be limited to those used by the author in preparation of the article. They should be typed on a special page at the end of the manuscript. The citation should include, in the order given, name of author, title of article (with subtitle), name of periodical, with volume, page, month—day of month if weekly or biweekly—and year. References to books must contain, in the order given, name of author, title of book, city of publication, name of publisher, and year of publication.

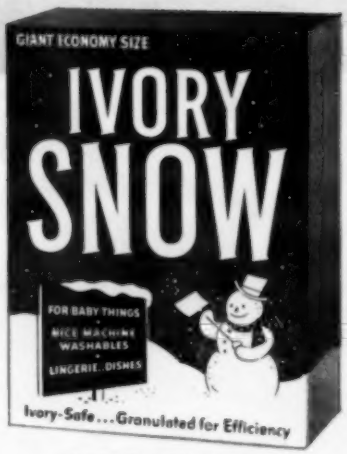
AMERICAN MEDICAL ASSOCIATION

535 North Dearborn Street **Chicago 10**

Why should you recommend Ivory Snow for baby's wash?



Because Ivory Snow is as safe and mild as soap can be . . . as pure a soap as mother can buy! Ivory Snow is Ivory-safe, leaves diapers and baby clothes soft, smooth... free from irritating deposits that can chafe tender skin. Granulated for washing machine efficiency, Ivory Snow is as practical for mother as it is safe for baby!



99 44/100% PURE® WITH BEAUTY GLOW

A Procter & Gamble Product

This After-School Snack

"Pays its way" in Protein, Vitamins, Minerals

Satisfaction of the child's after-school hunger need not come from low nutrient, high calorie foods.

Enriched Bread

—with its growth-promoting protein, B vitamins, iron, and calcium— as the vehicle for other foods contributes significantly to the child's nutritional needs.

AMERICAN BAKERS ASSOCIATION
20 North Wacker Drive Chicago 6, Illinois

Each 0.6 cc. of ABDEC DROPS supplies:

Vitamin A	5,000 units
Vitamin D	1,000 units
Vitamin C (ascorbic acid)	50 mg.
Vitamin B_1 (thiamine hydrochloride)	1 mg.
Vitamin B_2 (G) (riboflavin)	1.2 mg.
Vitamin B_6 (pyridoxine hydrochloride)	1 mg.
Pantothenic acid (as the sodium salt)	5 mg.
Nicotinamide	10 mg.
Vitamin B_{12}	2 mcg.

In bottles of 15 and 50 cc. with calibrated plastic droppers.

even Mary's not contrary when it's time for her delicious, apple-flavored

ABDEC® DROPS WITH VITAMIN B_{12}

comprehensive multivitamin formula

now with improved formula for even greater protection...

Vitamin B_{12} added

Nicotinamide doubled

Pantothenic acid more than doubled

Riboflavin tripled

MEDICAMENTA VERA

PARKE, DAVIS & COMPANY • DETROIT 32, MICHIGAN

47988

A NEW SERIES IN

SEX EDUCATION

Titles in the new series

- PARENTS' PRIVILEGE
  for parents of young children of pre-school and early school age
- A STORY ABOUT YOU
  for children in grades 4, 5, and 6
- FINDING YOURSELF
  for boys and girls of approximately junior high school age
- LEARNING ABOUT LOVE
  for young people of both sexes (about 16 to 20 years of age)
- FACTS AREN'T ENOUGH
  for adults who have any responsibility for children or youth that may create a need for an understanding of sex education

Prices of quantity orders of any SINGLE title

1 copy	$ .50
10 copies	4.25
25 copies	10.00
50 copies	18.75
100 copies	35.00
250 copies	81.25
500 copies	150.00

Prices of quantity orders of SETS

Single set	$ 2.25
10 sets	19.12
25 sets	45.00
50 sets	84.37
100 sets	157.50
250 sets	365.62
500 sets	675.00

Distributed by Order Department

AMERICAN MEDICAL ASSOCIATION

535 N. Dearborn St.

Chicago 10, Ill.

ORDER BLANK

Enclosed is $_____ (no stamps) for the following pamphlet(s):

Title	Quantity
1. PARENTS' PRIVILEGE	
2. A STORY ABOUT YOU	
3. FINDING YOURSELF	
4. LEARNING ABOUT LOVE	
5. FACTS AREN'T ENOUGH	
Complete set of five	

Please send pamphlet(s) to:
(Please Print)

Name_____

Street_____

City_____

Zone_____ State_____

CD-4-58

"Doctor, Tommy's thrown up three times!"

'Thorazine' promptly controls the vomiting of acute gastroenteritis. Even when vomiting has been protracted, the profound antiemetic effect of 'Thorazine' helps to restore food intake and hydration, thereby eliminating the need for parenteral fluids.

THORAZINE*

Especially for pediatric use:
'Thorazine' Syrup and 'Thorazine' Suppositories

Also available in tablets, ampuls, Spansule† capsules and the new 10 cc. (25 mg./cc.) multiple dose vials.

Smith Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F. †T.M. Reg. U.S. Pat. Off. for sustained release capsules, S.K.F.

FIRST BABY

early maternal tension:

FEEDING

early reassurance:

SIMILAC®

The primipara, even more than other mothers, is prone to emotional tension over her infant's diet: "Much of the anxiety about a new baby, particularly the first, centers in feeding. . . ."[1] This often means a cycle of tense mother-tense baby-tenser mother,[2] unless prevented or interrupted by the physician's guidance.

To reduce this formula tension effectively, specify Similac—particularly for the primipara. Similac is a physiologic feeding; it is simple to use; its dependable benefits reassure the at-first-uncertain mother.

1. Wright, F. H.: Journal-Lancet *77*:65, 1957.
2. Wagner, M. G.: J. Am. Dietet. A. *30*:329, 1954.

ROSS LABORATORIES
Columbus 16, Ohio

RESEARCH SERVICE Ross NUTRITION

PHYSICIANS COUNCIL

This advertisement conforms to the Code for Advertising of the Physicians' Council for Information on Child Health.

no pain
no memory
NO NIGHTMARE
OF FEAR
in pediatric anesthesia
PENTOTHAL Rectal is a painless, reliable and simple aid to anesthesia. As a premedication, it prevents emotional trauma in children and lessens dosage of inhalation agents–thus reducing postoperative nursing care.
Used as a basal anesthetic or as the sole agent in selected minor procedures, PENTOTHAL Rectal is a versatile and humane method in pediatric anesthesia. Abbott
PENTOTHAL® Sodium
(Thiopental Sodium, Abbott)
by rectum

YOUR
GUIDE TO
CURRENT PUBLICATIONS

Quarterly Cumulative Index Medicus

WITH AUTHORS AND SUBJECTS . . .

Divided into sections, one devoted to books and the other to periodical literature, the QUARTERLY CUMULATIVE INDEX MEDICUS contains a list of current publications alphabetized as to authors and subjects. The exact bibliographic reference is given under the author with titles in the original language, while titles under subjects are all in English. The index also includes a listing of journals, addresses and publishers.

The QUARTERLY CUMULATIVE INDEX MEDICUS appears twice a year; volumes are cloth bound and cover periodicals for six months as indicated on the publication. These two volumes will be a convenient and inclusive reference for current medical literature. Invaluable for practitioners, specialists, teachers, editors, writers, investigators, students and libraries.

SUBSCRIPTION PRICE $25.00 PER YEAR
CANADIAN AND FOREIGN $27.00 PER YEAR

AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET
CHICAGO 10, ILLINOIS

MEYENBERG GOAT MILK...
A FIRST CHOICE FOR INFANTS ALLERGIC TO COWS MILK...

FOR INFANTS allergic to cow's milk, Meyenberg Goat Milk is a medication of choice. Since the offending antigen in cow's milk is usually lactalbumin, a species-specific protein, goat milk has frequently proven a practical and successful substitute for cow's milk. Goat milk does not deprive the infant of the important values of milk.

Recent clinical findings indicate that the promiscuous use of milk-free substitutes is not without deleterious effects. Sensitivity to soy protein with cross sensitization to other legumes has been demonstrated. In addition, gastrointestinal disturbances with abnormal stools, diarrhea, sore buttocks, cramping and occasionally vomiting, have been reported following the ingestion of soybean containing preparations.***

In light of this evidence, for infants allergic to cow's milk, prescribe Meyenberg Goat Milk FIRST. It is nutritionally equal to cow's milk in protein, carbohydrates and fat . . . It contains no crude fibers or other extraneous material which may cause digestive upset. Meyenberg Goat Milk is rich in animal protein and accessory growth factors. Most important of all . . . it is not a milk substitute, but milk itself.

Evaporated in 14 fluid oz. cans, powdered in 14 oz. cans.

Write for a full can size sample to:

JACKSON-MITCHELL *Pharmaceuticals, Inc.*

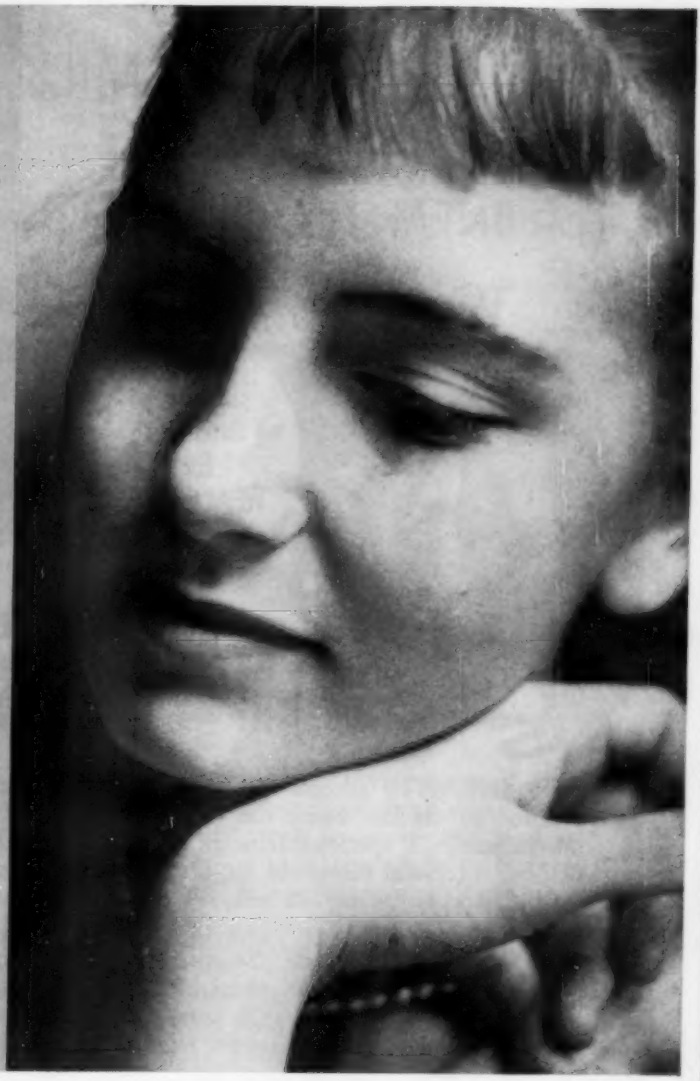
10401-A Virginia Avenue, Culver City, California. SINCE 1934

* Fries, J. H., Milk Allergy-Diagnostic Aspects and the Role of Milk Substitutes, J.A.M.A., Nov. 23, 1957.

** Ibid.

Write for a free reprint of this article.

the most precious gift in epilepsy



To have freedom from fear, to know security, to *feel* it, to have a sense of "belonging"... these are the hopes of the epileptic. Thanks to your knowledge and judicious use of modern antiepileptic therapy, these things are here today and every day of the epileptic's life. Here are five history making anticonvulsants which you can use to help treat the many forms of epilepsy. With them, you can give the most precious gift of all: a normal life. Abbott

PEGANONE®
(Ethotoin, Abbott)
Newest of Abbott's anticonvulsants . . . a new hydantoin of exceptionally low toxicity for *grand mal* and psychomotor seizures.

TRIDIONE®
(Trimethadione, Abbott)
PARADIONE®
(Paramethadione, Abbott)
Two eminently successful anticonvulsants for symptomatic control of *petit mal*, myoclonic and akinetic seizures . . . one will often work where the other won't.

PHENURONE®
(Phenacemide, Abbott)
Used with discretion, will often succeed where all other therapy fails in treating psychomotor, *grand mal*, *petit mal* and mixed seizures.

GEMONIL®
(Metharbital, Abbott)
An effective drug with low toxicity for treating *grand mal*, *petit mal*, myoclonic and mixed seizures symptomatic of organic brain damage.

ANTICONVULSANTS BY ABBOTT

803085

At any age

they welcome Ovaltine for extra nourishment

From pediatrics to geriatrics Ovaltine provides a rich source of the vitamins, minerals and other essential food elements required for the maintenance of a good nutritional state.

Ovaltine is a nourishing, well-tolerated beverage combining natural blandness with good taste. It produces a soothing and relaxing effect for the tense and nervous patient, particularly when taken at bedtime.

It is ideal for use where stimulating beverages should be avoided...ideal as nutritional fortification for patients on bland diets ...or to help maintain a satisfactory nutritional level during physiologic stress.

Three servings of Ovaltine and milk provide:

12 Vitamins		**13 Minerals**	
*Vitamin A	4000 I.U.	including Calcium, Phosphorus, Iron and Iodine	
*Vitamin D	420 I.U.	CARBOHYDRATE	65 Gm.
*Ascorbic acid	37.0 mg.	*PROTEIN	32 Gm.
*Thiamine	1.2 mg.	FAT	30 Gm.
*Riboflavin	2.0 mg.		
Pyridoxine	0.5 mg.		
Vitamin B_{12}	5.0 mcg.		
Pantothenic acid	3.0 mg.		
*Niacin	10.0 mg.		
Folic acid	0.05 mg.		
Choline	200 mg.		
Biotin	0.03 mg.		

*Nutrients for which daily dietary allowances are recommended by the National Research Council.

A jar of Ovaltine will be sent for your personal use on request.

Ovaltine® *when extra nourishment is desired*

The Wander Company, 105 W. Adams St., Chicago 3, Ill.

"Doctor, will you tell me . . ."

What are the symptoms?
How shall I treat it?
What causes it?

For practical information about communicable disease, have your patients read:

SCARLET FEVER
8 pages, 15 cents

IMMUNIZATION
by Ruth A. Thomas, 8 pages, 15 cents

WHOOPING COUGH
by Constance Frick, 4 pages, 10 cents

PNEUMONIA'S WATERLOO?
by William W. Bolton, 12 pages, 15 cents

WE CAN PREVENT DIPHTHERIA
by P. S. Rhoads, 8 pages, 15 cents

AMERICAN MEDICAL ASSOCIATION • 535 NORTH DEARBORN • CHICAGO 10

Here are several booklets on mental hygiene that may prove of interest and use to you and your patients.

EMOTIONAL HEALTH IN WORK AND PLAY
T. R. Retlaw, 8 pages, 15 cents

HYPNOTISM—HUMBUG OR HEALING
James A. Brussel, 6 pages, 10 cents

YOUR STAKE IN MENTAL HEALTH
George S. Stevenson, 4 pages, 10 cents

THE PSYCHIATRIST Edward Dengrove and Doris Kulman, 6 pages, 10 cents

BOOKLETS ON MENTAL HYGIENE

Keep a supply of these booklets on hand. Available at lower cost for quantity purchases.

AMERICAN MEDICAL ASSOCIATION
535 North Dearborn Street • Chicago 10 • Illinois

Combine your own clinical experience with the knowledge of experts . . .

by reading

- **A.M.A. Archives of DERMATOLOGY**
- **A.M.A. Archives of PATHOLOGY**
- **A.M.A. Archives of INDUSTRIAL HEALTH**

Write To:
Subscription Department

American Medical Association
535 N. Dearborn Street
Chicago 10, Ill.

A.M.A. SPECIALTY JOURNALS REACH THE CORE OF SPECIALIZED PRACTICE . . . *Subscribe NOW to:*

→ A.M.A. Archives of INTERNAL MEDICINE
→ A.M.A. Archives of PATHOLOGY
→ A.M.A. Archives of OPHTHALMOLOGY

Write to:

THE AMERICAN MEDICAL ASSOCIATION
535 North Dearborn Street
Chicago 10, Illinois

A.M.A JOURNAL OF
DISEASES OF CHILDREN

Poliovirus Neutralizing Antibody Levels in Pediatricians and Preclinical Faculty Members

PAUL F. WEHRLE, M.D.; GERSON ARONOVITZ, M.D.; ROBERT ZECHNICH, M.D., and PAUL PARKMAN, M.D., Syracuse, N. Y.

Considerable data are available which indicate that poliovirus infections are readily communicable under natural conditions in the general population. The age distribution of clinical cases of the disease in previous years has resembled that of measles [1] closely. This suggests that inapparent infections are widely disseminated, thus producing similar patterns of increasing resistance to both of these infections among older persons. This similarity, together with more direct methods of measurement,[2,3] may indicate that from 60 to 1000 silent infections occur in proportion to each recognized clinical case and that the frequency of clinical expression may vary with the age of the persons infected.

In addition to the evidence for widespread infection with the three recognized immunologic types of poliovirus, the socioeconomic level [4-8] appears to influence the dissemination of these viruses. Evidence of previous infection with poliovirus has been found to be more prevalent under conditions of poor hygiene and among lower socioeconomic groups. Close contact in family groups also appears to favor transmission of the infection. The infection rate in families has been found to be as high as 100% in recent studies when determined by antibody measurements and virus isolation among susceptible household case contacts.[9-12]

In spite of the widespread occurrence of poliovirus and the ease of its transmission in the home situation, it is apparent that the agent is not always readily transmitted, even under conditions which may seem ideal. During intense epidemic situations latent epidemization of the community does not appear to be complete.[13-15] Among nursery school contacts the infection has been described as following a rather "narrow stream." [16] A similar pattern has been observed during an outbreak localized to an apartment house.[17] Transfer of infection to hospital personnel caring for acute poliomyelitis patients, as measured by changes in the presence or level of neutralizing antibodies, has not been demonstrated either under epidemic [18] or endemic [19] conditions.

It was believed that further information on the conditions which may influence the communicability of poliovirus could be obtained from a serological survey of a sample of pediatricians. These persons often enter homes of different socioeconomic groups and of varying conditions of sanitation. In these situations and in office practice, they may be

Received for publication Dec. 21, 1957.

Supported by a Grant (E-1256) from the National Institutes of Health, Public Health Service.

Department of Pediatrics, State University of New York College of Medicine, Syracuse, and the Syracuse City Hospital. Junior Public Health Interns, New York State Department of Health (Drs. Aronovitz and Parkman); Medical Student Fellow of the National Foundation for Infantile Paralysis (Dr. Zechnich).

in close contact with young children experiencing either clinical or subclinical infections with polioviruses.

Methods

A group of 20 physicians (19 pediatricians) in practice in Syracuse, N. Y., was selected as the test group. Eighteen were voluntary or part-time members of the Department of Pediatrics, State University of New York in Syracuse. One physician who cared for many children in the course of an active general practice was also included. All were in active private practice, including house calls, with the exception of two of the pediatricians. These two came in contact with large numbers of children during hospital outpatient and clinic activities.

The control group consisted of 20 persons engaged in various full-time academic activities in the preclinical departments of the same medical school. This group consisted almost entirely of persons with either a Ph.D. or an M.D. academic preparation. The criteria for selection were a regular full-time faculty appointment in one of the preclinical departments and no clinical contact with patients.

An initial blood sample was obtained from all study subjects in July, 1956. A second sample was obtained four months later, during the latter part of November, 1956. No stool samples were collected, nor were other methods of virus isolation attempted.

The clear sera obtained were inactivated for one hour at 60 C and stored at —20 C until tested. Twofold serial dilutions of paired sera from 1:4 to 1:4000 were challenged simultaneously with equal volumes of tissue culture fluid containing approximately 100 ID_{50} of Mahoney (Type I), M E F_1 (Type II) and Leon (Type III) poliovirus. The virus used was the first monkey kidney tissue culture passage of strains obtained originally from the Connaught Medical Laboratories, Toronto, Canada. The serum-virus mixtures were shaken and then allowed to stand for one hour at 25 C before trypsinized monkey kidney cells[20] were added. Control sera were included to insure comparability with previous and subsequent tests. The virus dose selected was controlled by half-log base 10 titrations, with use of four tubes per dilution. The metabolic inhibition technique[21] was used to determine the end-points. End-points were also checked microscopically. The highest dilution of serum protecting against the cytopathogenicity of the virus was considered the end-point, when the two methods were at variance.

Exposure of Study Groups to Poliovirus Infection.—It is difficult to evaluate the exposure of the pediatrician group during the study period. Although an intense outbreak of poliomyelitis occurred near Syracuse, only four cases originated within the city and surrounding county during the latter part of 1956. However, data previously presented[4,6,7,22] suggest that clinical cases may not be an entirely reliable index of the extent of inapparent infection. It is difficult to believe that the viruses were absent from this community during the study period and that opportunity for contact with subclinical infections was lacking in either this or previous years.

Most of the pediatricians had been in practice for five years or more in this area, and half of them, for 10 years or longer. During the previous 10 years a total of 869 cases of poliomyelitis were reported from Syracuse and Onondaga County. Nearly half of these cases were reported to be paralytic. The mean number of cases per year was 87, and the median, 71. The smallest number of cases reported during this interval (with the exception of the study year) was 28, while the year of greatest incidence was 1950, with 214 cases. These represent rates of from 7.5 to 57 per 100,000, with a mean rate of 23.* Only one pediatrician denied contact with clinical poliomyelitis cases during previous years. Nine had between two and five years of clinical poliomyelitis experience, and the remaining ten had cared for at least one polio patient per year for six years or more.

Since naturally acquired neutralizing antibody has been shown to persist at high levels for many years,[23] it seemed reasonable to expect that effective exposure of the study subjects during these years should be reflected by the presence of neutralizing antibodies in titers of 1:4 or higher.

Results

Since the validity of the present study depends largely on the comparability of the two groups in all respects other than the presence or absence of contact with large numbers of potentially infected children under varying conditions of hygiene, health, and disease, some of the variables are summarized in the first three tables.

In Table 1 the ages of the participants are recorded by age group. As noted, the distributions are remarkably similar. All study members were males, with one exception, and all were Caucasian. Four of the basic science faculty were foreign-born, as was one of the pediatrician group. Nine of

* Data provided by Dr. A. C. Silverman.

TABLE 1.—*Age Distribution of Study Participants by Professional Classification*

Age Group, Yr.	Professional Category		Totals
	Pediatricians, No.	Scientists, No.	
30–34	7	6	13
35–39	7	5	12
40–44	3	6	9
45–49	1	2	3
50+	2	1	3
Totals	20	20	40

the pediatricians and eight of the scientists tested had resided in Syracuse for more than 10 years. Two persons in each group had lived in foreign countries for variable periods during the preceding 10 years. One pediatrician had a history of possible nonparalytic poliomyelitis several years earlier, although this had not been confirmed by either spinal fluid or other laboratory data. One scientist had a history of family contact with a case of clinical poliomyelitis of unknown type during his childhood. Activities of the wives with children's groups was surprisingly similar. Ten of the physicians' wives and seven of the scientists' wives were working with cub scouts, church groups, or similar organizations.

The number of children in the families of study members and the ages of the children are recorded in Tables 2 and 3. Again, there is a remarkable similarity both in the numbers of children per family unit and in their age distribution. While there may be important differences between these two groups, the only major differences apparent among the variables examined were (1) the quantity and type of professional contact with young children who may serve as effective sources of infection and (2) a history of treating patients with poliomyelitis during previous years.

The neutralizing antibody titers present in the initial sera are shown in Table 4. Although each serum was tested at serial twofold levels, the data so obtained have been combined into fourfold groups for brevity in presentation. It is apparent that the distribution of neutralizing antibody appears to be strikingly similar for the two groups in respect to the level as well as the presence of antibody at the 1:4 level. A significant proportion of each group lacks demonstrable antibody at the 1:4 level. Only one pediatrician and three persons in the scientist category lacked all three types of antibody, and only four and three persons, respectively, lacked two of the three types. It should be noted that two pediatricians had received a single injection of poliomyelitis vaccine (scheduled to be discarded) of unknown lot number, a short time prior to the initiation of the study, while a third had received two injections. These are indicated in Table 4.

TABLE 2.—*Size of Families of Study Participants by Professional Classification*

Total No. of Children per Family	Professional Classification					
	Pediatricians		Scientists		Totals	
	Families, No.	Total Children	Families, No.	Total Children	Families, No.	Total Children
0	0	0	4	0	4	0
1	6	6	1	1	7	7
2	3	6	4	8	7	14
3	7	21	6	18	13	39
4	2	8	3	12	5	20
5	1	5	1	5	2	10
6	1	6	1	6	2	12
Totals	20	52	20	50	40	102

TABLE 3.—*Age Distribution of Children in Households of Study Participants*

Age of Children, Yr.	Professional Classification of Head of Household		Totals
	Pediatrician	Scientist	
0–4	19	18	37
5–9	21	17	38
10–14	6	13	19
15+	6	2	8
Totals	52	50	102

TABLE 4.—*Initial Serum Neutralizing Antibody Titer in Pediatricians (Ped.) and Scientists (Sci.) by Poliovirus Type and Professional Classification*

Neutralizing Antibody Level *	Antibody Presence by Type								
	Type I			Type II			Type III		
	Ped.	Sci.	Total	Ped.	Sci.	Total	Ped.	Sci.	Total
<4	7 †	7	14	4	5	9	9 †	8	17
4–8	5	2	7	1	0	1	3	2	5
16–32	3	6	9	4	4	8	2	6	8
64–128	1	4	5	6	8	14	5 †‡	3	8
256–512	4 †‡	1	5	5 †††‡	3	8	1	1	2
Totals	20	20	40	20	20	40	20	20	40

* Number is reciprocal of serum dilution.
† Previous single injection of 1 ml. of poliomyelitis vaccine (two participants).
‡ Two injections of 1 ml. of poliomyelitis vaccine prior to study (one participant).

This Table has been condensed further to illustrate the serological similarities of the groups. In Table 5 the results of all three neutralization tests have been combined into three categories: negative (<1:4 serum dilution), low (1:4 to 1:32) and high (1:64 or more). The similarity again is striking.

TABLE 5.—*Initial Serum Neutralizing Antibody Levels for Three Types of Poliovirus by Professional Category*

Neutralizing Antibody Level *	Antibody Presence for All Three Types Combined †		Totals
	Pediatricians	Scientists	
<4	20 (2)‡	20	40
4-32	18	20	38
64+	22 (7)‡	20	42
Totals	60 (9)‡	60	120

* Number is reciprocal of serum dilution.
† Since there are three types of virus, each person appears as three tests in this table.
‡ Number in parenthesis refer to persons with one or two previous poliomyelitis vaccine inoculations (three persons with three types tested).

One-third of the neutralization tests in each study group failed to demonstrate antibodies at the 1:4 level.

It is difficult to evaluate the relation of antibodies to age groups, since all participants were 30 or more years of age, with only three older than 50 years. When the subjects are divided into two groups, i. e., those less than 40 years of age and those more than 40 years (Table 6), the anticipated trend toward increased antibody prevalence with increasing age in the scientist and total groups is evident, albeit not very impressive. Persons with large families were distributed among both age levels in a pattern similar to that in the total study population, and so this was not an important factor.

Further correlations were attempted between the presence of antibodies and the number of children in the household. As shown in Table 7, absence of antibodies at the 1:4 or higher levels occurred approximately twice as often among those with none or a single child as among those with four or more children. These differences appear to be of borderline significance ($\chi^2=3.8$; $P=0.05$). The age of the study subject did not influence this finding, since six of the nine persons with four or more children were less than 40 years of age, a distribution similar to that of the entire group.

TABLE 6.—*Levels of Neutralizing Antibody Against Three Types of Poliovirus by Age Group of Subject*

Serum Neutralizing Antibody Titer	Professional Classification								
	Pediatricians			Scientists			Total		
	<40 *	40+ *	Totals	<40	40+	Totals	<40	40+	Totals
<4	12	6	18	15	5	20	27	11	38
4-32	11	7	18	10	10	20	21	17	38
64+	10	5	15	8	12	20	18	17	35
Totals	33	18	51 *	33	27	60	66	45	111

* The three subjects who had received poliomyelitis vaccine inoculations were deleted from this table.

TABLE 7.—*Presence of Neutralizing Antibody Against Each of Three Types of Poliovirus in Relation to Family Size, Pediatricians and Scientists Combined*

Children, No.	Neutralizing Antibody Status *				
	<4	4–32	64+	Total	%<4
0–1	14	8	8	30	46.7
2–3	18	20	16	54	33.3
4+	6	10	11	27	22.2
Totals	38	38	35	111 †	34.2

* Number is reciprocal of serum dilution. χ^2-Test comparing category 0–1 and 4+ is 3.8; P=0.05.
† Deletion of three persons with one or more poliomyelitis vaccine inoculations.

When the data were analyzed by the ages of the children (i. e., school age or preschool), there was no positive correlation with the presence or absence of paternal antibody. No correlation was noted between a single type of antibody and the presence of children. Unfortunately, the majority of the wives of study members had been immunized before these data were analyzed, and so it was impossible to determine whether the differences ascribed to the numbers of children in the household would have been similar, or possibly even greater, among the wives.

No significant changes in the antibody levels of unimmunized subjects were observed during the study period. Two scientists and twelve pediatricians received one or more injections of various lots of poliomyelitis vaccine when the priority allocation was relaxed during the latter part of 1956. Since the number immunized was small and different lots of vaccine had been used, the response of this group was not evaluated; all but one of these vaccinees had naturally acquired antibodies of at least one type.

Comment

In evaluating the distribution of antibodies in the two groups, the first question to be answered is whether the groups are truly comparable. In terms of national origin, age, sex, race, duration of residence in Syracuse, family size, and composition by age the groups appear remarkably similar. The training periods for both groups may be considered similar in many respects. No member of either group had had laboratory experiences with poliovirus. Three members of the department of pathology may have had contact with contaminated material during occasional autopsies on poliomyelitis patients. The serological status of these three persons did not differ from that of the group as a whole. Although there may be other differences, the most obvious ones are the pediatricians' frequent and close professional contact with children and their treatment of patients with clinical poliomyelitis.

The second question concerns the opportunity for exposure of the pediatrician group to poliovirus infection during house calls, office and clinic visits, and in the hospital. If sufficient numbers of poliovirus strains are prevalent among the childhood population, the conditions of exposure of the pediatricians should permit frequent virus transfer. Although the clinical case rate in the Syracuse area has not been unusually high in recent years, sufficient data are available [6,7,22] which suggest that large numbers of children had inapparent infections during this period.

The pediatricians may be at somewhat greater risk of infection on theoretical grounds than the hospital populations which were studied previously,[18,19] since poliovirus infections may be encountered by the pediatrician at an earlier stage. Of equal importance, hand washing and other sanitary precautions may be more difficult to accomplish during home visits than in the hospital.

The third problem in evaluating the serological findings is whether effective exposure to polioviruses may be recognized by neutralizing antibody determinations months or years later. A second and related question is whether naturally acquired infections with increases in antibody titers take place in the presence of neutralizing antibody.

In regard to the persistence of antibody, a serological survey [23] of an Eskimo population 19 years after infection demonstrated than antibody was not only present in essentially all exposed persons but was main-

tained at relatively high levels with the exception of the older persons. Although neutralizing antibody levels decline and may even revert to undetectable levels,[22] the latter does not appear to occur very often.

Low or undetectable levels of passively acquired antibodies do not appear to prevent experimental infection in chimpanzees [24] or naturally acquired infection in man.[25,26] Homotypic and heterotypic increases in antibody levels in actively immunized chimpanzees have been observed following experimental infections.[27] Previous naturally acquired antibody has not entirely prevented enteric infection in man with subsequent neutralizing antibody increases either under experimental conditions with use of attenuated polioviruses [28] or under natural conditions of exposure during an interepidemic period.[12,29]

These several considerations suggest that the data presented appear to be consistent with approximately equal effective exposure to polioviruses among members of the two groups, although the groups are considerably different regarding potential exposure. Since the pediatrician group is somewhat unique in that it is working closely with children of all social strata, at times under conditions which do not permit optimal "hospital" hygiene, our data suggest that this infection is not readily transmitted, except within the household, even in its early stages. It also would appear to offer further evidence against air-borne transmission.[30]

Qualitative tests by Dr. W. McD. Hammon for detecting the presence of neutralizing antibodies among 21 staff medical officers at Clark Air Force Base, Philippines, and 17 California physicians indicated that only 49%, 55%, and 57% had demonstrable Type I, II, and III poliovirus neutralizing antibodies, respectively.[31] A survey of neutralizing antibodies in two physicians and their families and the children of five other physicians in Geneva, Switzerland,[32] revealed that antibodies were as frequent among them as in control families residing in the same area. These data are similar to those of the present study.

The relationship of the presence of antibody in the subject to the number of children in his household provides additional information regarding a potential source of adult infection. The important role of children in the dissemination of poliovirus infection within a community has been suspected on the basis of the rising age group of patients during epidemics,[33] the ages of initial and subsequent cases in multiple-case families,[34] and more direct measurements with serological and virus-isolation techniques during localized outbreaks.[14,16,17] Family size has been suggested as a factor in the presence of neutralizing antibody [4,13,14] as well as in the acquisition of infection in an anterospective study.[11,29] However, socioeconomic differences leave this association open for further investigation.[29] Changes in clinical attack rates to involve females more frequently after puberty and complement-fixation studies suggest that wives may be more frequently infected than husbands.[12] This may in turn reflect the mother's more intimate exposure to her young children.

The data presented here suggest that the busy pediatrician may be at greater risk of effective poliovirus exposure from his own children than from his practice. However, it should be pointed out that precise measurements of the actual risk of clinical poliomyelitis are not possible from studies of this nature. Indeed, recent studies [35] based on small numbers of persons indicate that physicians may be at somewhat greater risk than the general population. Whether this is properly correlated with family size, socioeconomic status, or activities of practice is not clear.

Summary

Poliovirus neutralizing antibody levels in a group of pediatricians were determined and compared with those of a control group of scientists living in the same community. The two groups appeared comparable in all

respects except that the pediatricians had considerable professional contact with children and poliomyelitis patients.

Presence of antibody at the 1:4 level was equal in the two groups, as was the distribution of titers in those with greater antibody levels. No significant changes in titer were observed during the summer of 1956. A positive correlation was obtained between the number of children in the household and the presence of antibody in the study participants.

These data suggest that poliovirus infection is not easily transferred to pediatricians under normal conditions of practice.

The correlation between the number of children in his household and the presence of neutralizing antibody in the subject suggests that household contact with his own children may have been more important in effectively introducing infection to the pediatrician than the activities of his practice.

Department of Pediatrics, Syracuse Memorial Hospital (10).

REFERENCES

1. Howe, H. A.: Epidemiology of Poliomyelitis in the Light of Modern Research, Am. J. Med. 6:537-550, 1949.

2. Melnick, J. L.: Poliomyelitis in Urban Sewage in Epidemic and in Nonepidemic Times, Am. J. Hyg. 45:240-253, 1947.

3. Melnick, J. L., and Ledinko, N.: Development of Neutralizing Antibodies Against the Three Types of Poliomyelitis Virus During an Epidemic Period: The Ratio of Inapparent Infection to Clinical Poliomyelitis, Am. J. Hyg. 58: 207-222, 1953.

4. Hammon, W. McD.; Sather, G. E., and Hollinger, N.: Preliminary Report of Epidemiological Studies on Poliomyelitis and Streptococcal Infections: Lansing Neutralizing Antibody and Antistreptolysin "O" Surveys of California Cities, Texas, North Carolina, Mexico, Pacific Islands, and Japan, Am. J. Pub. Health 40:293-306, 1950.

5. Paul, J. R.; Melnick, J. L., and Riordan, J. T.: Comparative Neutralizing Antibody Patterns to Lansing (Type 2) Poliomyelitis Virus in Different Populations, Am. J. Hyg. 56:232-251, 1952.

6. Melnick, J. L.; Paul, J. R., and Walton, M.: Serologic Epidemiology of Poliomyelitis, Am. J. Pub. Health 45:429-437, 1955.

7. Honig, E. I.; Melnick, J. L.; Isacson, P.; Parr, R.; Myers, I. L., and Walton, M.: An Epidemiological Study of Enteric Virus Infections; Poliomyelitis, Coxsackie and Orphan (ECHO) Viruses Isolated from Normal Children in Two Socioeconomic Groups, J. Exper. Med. 103:247-262, 1956.

8. Coriell, L. L.; Schaeffer, K.; Felton, H. M.; Fernandez-Moran, H., and Bierly, M. Z.: A Serologic and Clinical Survey of Poliomyelitis in Caracas, Venezuela and Galveston, Texas, and the Response to Salk Vaccine, Am. J. Pub. Health 46:1431-1438, 1956.

9. Bodian, D., and Paffenbarger, R. S., Jr.: Poliomyelitis Infection in Households: Frequency of Viremia and Specific Antibody Response, Am. J. Hyg. 60:83-98, 1954.

10. Brown, G. C.; Rabson, A. S., and Schieble, J. H.: The Effect of Gamma Globulin on Subclinical Infection in Familial Associates of Poliomyelitis Cases: I. Quantitative Estimation of Fecal Virus, J. Immunol. 73:54-61, 1954.

11. Fox, J. P.; Gelfand, H. M.; Bhatt, P. N.; LeBlanc, D. R., and Conwell, D. P.: Immunizing Infections with Poliomyelitis Viruses and Seroimmune Patterns in Southern Louisiana, Ann. New York Acad. Sc. 61:968-978, 1955.

12. Hammon, W. McD.; Ludwig, E. H.; Sather, G. E., and Schrack, W. D.: A Longitudinal Study of Infection with Poliomyelitis Viruses in American Families on a Philippine Military Base During an Interepidemic Period, Ann. New York Acad. Sc. 61:979-988, 1955.

13. Melnick, J., and Ledinko, N.: Social Serology: Antibody Levels in a Normal Young Population During an Epidemic of Poliomyelitis, Am. J. Hyg. 54:354-382, 1951.

14. Nolan, J. P.; Wilmer, B. H., and Melnick, J. L.: Poliomyelitis: Its Highly Invasive Nature and Narrow Stream of Infection in a Community of High Socioeconomic Level, New England J. Med. 253:945-954, 1955.

15. Wehrle, P. F.; Hammon, W. McD.; Coriell, L. L., and McAllister, R. M.: Spread of Poliovirus Infection During an Epidemic of Unusual Severity, Am. J. Hyg. 65:386-403, 1957.

16. McCarroll, J. R.; Melnick, J. L., and Horstmann, D. M.: Spread of Poliomyelitis Infection in Nursery Schools, Am. J. Pub. Health 45:1541-1550, 1955.

17. Melnick, J. L.; McCarroll, J. R., and Horstmann, D. M.: A Winter Outbreak of Poliomyelitis in New York City, Am. J. Hyg. 63:95-114, 1956.

18. Arnold, J. H.: Personal communication to the authors.

19. Wehrle, P. F.: The Risk of Poliomyelitis Infection Among Exposed Hospital Personnel, Pediatrics 17:237-246, 1956.

20. Dulbecco, R., and Vogt, M.: Plaque Formation and Isolation of Pure Lines with Poliomyelitis Viruses, J. Exper. Med. 99:167-182, 1954.

21. Salk, J. E.; Younger, J. S., and Ward, E. N.: Use of Color Change of Phenol Red as the Indicator in Titrating Poliomyelitis Virus or Its Antibody in a Tissue Culture System, Am. J. Hyg. 60:214-230, 1954.

22. Turner, T. B.; Hollander, D. H.; Buckley, S.; Kokko, U. P., and Winsor, C. P.: Age Incidence and Seasonal Development of Neutralizing Antibodies to Lansing Poliomyelitis Virus, Am. J. Hyg. 52:323-347, 1950.

23. Paul, J. R.; Riordan, J. T., and Melnick, J. L.: Antibodies to 3 Different Antigenic Types of Poliomyelitis Virus in Sera from North Alaskan Eskimos, Am. J. Hyg. 54:275-285, 1951.

24. Bodian, D.: Experimental Studies on Passive Immunization Against Poliomyelitis: III. Passive-Active Immunization and Pathogenesis After Virus Feeding in Chimpanzees, Am. J. Hyg. 58: 81-100, 1953.

25. Hammon, W. McD.; Coriell, L. L.; Ludwig, E. H.; McAllister, R. M.; Greene, A. E.; Sather, G. E., and Wehrle, P. F.: Evaluation of Red Cross Gamma Globulin as a Prophylactic Agent for Poliomyelitis: V. Reanalysis of Results Based on Laboratory Confirmed Cases, J. A. M. A. 156: 21-27, 1954.

26. Brown, G. C.; Rabson, A. S., and Schieble, J. H.: The Effect of Gamma Globulin on Subclinical Infection in Familial Associates of Poliomyelitis Cases: II. Serological Studies and Virus Isolations from Pharyngeal Secretions, J. Immunol. 74:71-80, 1955.

27. Howe, H. A.: Studies of Active Immunogenesis in Poliomyelitis: I. Persistence and Recall by Homotypic or Heterotypic Superinfection of Neutralizing Antibody Originally Induced in Chimpanzees by Vaccination or Infection, Am. J. Hyg. 60:371-391, 1954.

28. Sabin, A. B.: Immunization of Chimpanzees and Human Beings with Avirulent Strains of Poliomyelitis Virus, Ann. New York Acad. Sc. 61:1050-1058, 1955.

29. Gelfand, H. M.; LeBlanc, D. R.; Fox, J. P., and Conwell, D. P.: Studies on the Development of Natural Immunity to Poliomyelitis in Louisiana: II. Description and Analysis of Episodes of Infection Observed in Study Group Households, Am. J. Hyg. 65:367-385, 1957.

30. Faber, H. K.: The Pathogenesis of Poliomyelitis, a monograph in American Lectures in Pediatrics, Springfield, Ill., Charles C Thomas, Publisher, 1955.

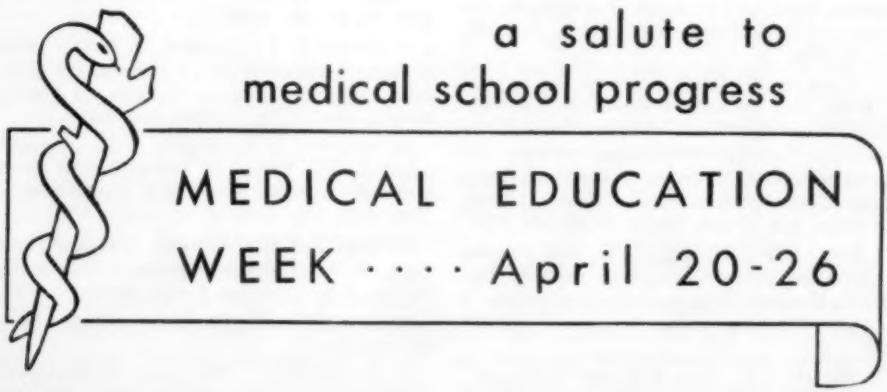
31. Hammon, W. McD.: Personal communication to the authors.

32. DuPan, R. M.; Paccaud, M.; Weisflog, G., and Hammon, W. McD.: Étude des anticorps antipoliomyélitiques dans certaines familles de Genève, en particulier dans des familles de médecins, Schweiz. Med. Wchnschr. 27:779-782, 1956.

33. Gamma Globulin in the Prophylaxis of Poliomyelitis: Report of the National Advisory Committee for the Evaluation of Gamma Globulin in the Prophylaxis of Poliomyelitis, Public Health Monograph, No. 20, U. S. Department of Health, Education, and Welfare, Public Health Service, 1953.

34. Lindahl, J.: The Poliomyelitis Epidemic in Stockholm, 1953: II. Family Infections, Acta med. scandinav. 154 (Supp. 316):15-19, 1956.

35. Doll, R., and Hill, A. B.: Deaths from Poliomyelitis Among British Doctors, Brit. M. J. 1:372, 1957.



Vaccination Against Poliomyelitis

Its Present and Future Status

LEWIS L. CORIELL, M.D., Camden, N. J.

Fewer cases of poliomyelitis were reported in the United States in 1957 than in any year since 1942. This is the third consecutive year that the number of cases has declined, which is unusual by itself, but the fact that this progressive decline in reported cases is accompanied by a decrease in paralytic rate and coincides with the increasingly widespread use of the Salk vaccine is widely accepted as proof that the vaccination program is responsible for the decline.

This may be true, but all physicians are aware of the erratic and unpredictable behavior of poliomyelitis in the past and therefore wish to examine without bias or emotion the facts which have been presented by the most recent poliomyelitis season in order that logical recommendations and advice can be given in 1958. To this end, the present report contains partial and provisional epidemiologic data for 1957 and related information which may be useful.

The only controlled study of the effectiveness of poliomyelitis vaccine in this country was reported by Francis [1] in the field studies of 1954 and showed 60% to 70% protection against poliovirus Type 1 infection and 80% to 90% protection against infection with poliovirus Types 2 and 3. No significant protection was noted against nonparalytic poliomyelitis. In a small controlled study in England, Hill [2] reported only 1 case in approximately 150,000 vaccinated children and 6 cases in a similar number of controls. This is too small a study to be convincing but it is in agreement with the Francis report.

Epidemiologic data on poliomyelitis in the United States during 1955,[3] 1956,[4] and 1957 [5] are not controlled studies and are therefore subject to error, but they are nevertheless valuable when carefully analyzed. They suggest a 75% to 80% reduction of paralytic poliomyelitis in all vaccinated persons, with close to 90% protection in those who have received three doses of vaccine. It is the function of the National Poliomyelitis Surveillance Program of the Communicable Disease Center of the Public Health Service to collect and disseminate epidemiological data on the safety and effectiveness of poliomyelitis vaccine. All physicians are referred to the reports for 1955 [3] and 1956 [4] and to the provisional reports for 1957,[5] some of which will be quoted below. These reports are the product of a well-planned program for rapid collection and analysis of epidemiologic data through local, state, and national health departments and are in themselves a major advance in the technique of public health as it relates to epidemic disease control.

It is useful to examine the incidence of poliomyelitis over the years as a background for the present discussion. This information is presented in Figure 1, showing the number of diagnosed cases per year per 100,000 population from 1912 to 1957. Note the progressive increase in cases from 1942 through 1952. This upward trend in incidence gives way to a consistent decline for

Submitted for publication Jan. 14, 1958.

Aided by a grant from the National Foundation for Infantile Paralysis.

Read at the Annual Clinical Meeting of the American Medical Association, Philadelphia, Dec. 4, 1957.

Medical Director, Camden Municipal Hospital for Contagious Diseases, and Research Director, South Jersey Medical Research Foundation.

the years 1955, 1956, and 1957, which has no precedent in previous experience except for the years 1917, 1918, and 1919, immediately following the 1916 epidemic.

There have been 5633 cases of poliomyelitis reported to the Public Health Service so far this year, through Nov. 15, compared with 14,463 for the same period in 1956, with 27,529 in 1955, and with over 52,000 in 1952. The cumulative totals this year are the lowest since 1942. The total number of paralytic cases through Nov. 15 was 1988, compared with 6196 in 1956 and 9796 in 1955 for the same period.

Fig. 1.—Annual poliomyelitis incidence rates per 100,000 population in the United States from 1912 to 1957. The 1957 rate is provisional data reported up to Nov. 15.

No large epidemic of poliomyelitis has occurred this year in any state or territory, which is a sharp departure from experience in the last 15 years, when major epidemics have occurred in one or more sections of the country each year. During the last 15 years poliomyelitis in any specific geographic area has occurred in epidemic proportions at intervals separated by several years of low incidence, but at no time has the whole country been free from localized epidemic outbreaks for a whole year. Only three states and the District of Columbia have reported more cases than in the same period of 1956. They are South Dakota, with a case rate of 6 per 100,000 population; South Carolina, with a rate of 6; Tennessee, with a rate of 4, and District of Columbia, with a case rate of 8. These are figures for the state as a whole, but all are far from the epidemic incidence of 20/100,000.

TABLE 1.—*Percentage Distribution by Age Groups of Paralytic Poliomyelitis in the United States by Years* *

Age Group	Percentage Distribution of Paralytic Poliomyelitis			
	1952	1955	1956	1957
0–4	29	22	42	46
5–9	24	21	16	16
10–14	13	12	11	7
15+	33	34	32	31

* Based on provisional data (CDC Surveillance Report No. 133).

Age Distribution

The altered age distribution noted in 1956 has continued in 1957, as shown by provisional and incomplete data. Specifically, this change is an increase in the percentage of paralytic cases in the birth to 4-year age group, with a compensatory decline in the 5- to 9- and the 10- to 14-year age groups, without much change in the percentage of paralytic cases in adults. This trend is illustrated in Table 1.[5]

Since the total number of cases has actually decreased in all groups, the relative increase in percentage of cases occurring in the birth to 4-year age group may reflect the greater reduction of paralytic polio in the school-age children, who have been more intensively vaccinated during the last three years. In 1956 the reduction was greatest for the 8- and 9-year-olds, who had been vaccinated as first and second graders in the

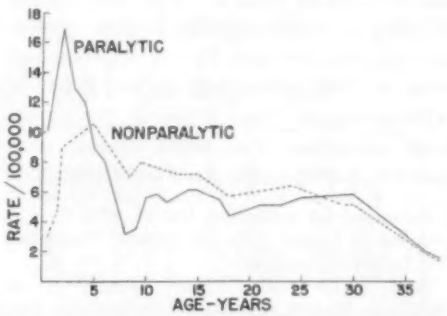


Fig. 2.—Age distribution of poliomyelitis in the United States in 1956 from preliminary data from 45 states.[6] Note the reduction in paralytic disease among 8- and 9-year-olds, without a compensatory decrease in nonparalytic disease.

TABLE 2.—*Paralytic and Nonparalytic Poliomyelitis 1951-1957*

Type of Diagnosis	Per Cent of Total Cases Reported						
	1957 *	1956	1955	1954	1953	1952	1951
Paralytic	37	44	48	48	44	37	36
Nonparalytic	61	38	43	34	34	22	19
Unclassified	2	18	9	18	22	41	45

* Provisional and incomplete data to Sept. 1, 1957.[1]

spring of 1955 and revaccinated in the spring of 1956 (Fig. 2).

Paralytic and Nonparalytic Cases

Provisional data reported to the Public Health Service up to Sept. 1, 1957, show that 37% of the reported cases were paralytic, 61% were nonparalytic, and 2% were unclassified. These figures may well change when final data for the whole year can be analyzed. A trend of recent years has continued in 1957, namely, the classification of reported cases as either paralytic or nonparalytic (Table 2). This more complete reporting was given impetus by the γ-globulin studies and later by the vaccine studies but is largely the result of the hard work, teamwork, and educational program of the Polio Surveillance Unit in following up the reported cases.

Geographic Pattern

Every state and territory reported fewer cases of poliomyelitis in 1957 than the average annual number during the previous five years. Many hospitals reported no cases of poliomyelitis this year, and others, the smallest number on record. No area experienced a sharp outbreak of epidemic proportions. The majority of cases this year occurred in the southern states and the north central states.

TABLE 3.—*Production and Use of Poliomyelitis Vaccine, 1955-1957*

Year	Vaccine Produced, Ml.	No. Vaccinated	Recipients
1955	27,667,000	10,000,000	1st and 2d graders
1956	77,043,000	35,000,000	Patients under 20
1957	95,538,000	27,000,000	Children and adults
Total	200,248,000	72,000,000	

The age distribution pattern of paralytic poliomyelitis was associated with the geographic region as follows: the percentage of cases in the 0- to 4-year-old children was 63%, 61%, and 62% in the south-east, south central, and Hawaii-Puerto Rico areas, respectively, while in the north-east, north central, and north-west states 43% to 48% of cases occurred in adults.

Use of Vaccine

It is estimated that there are 109,000,000 persons under 40 years of age in the United States and that 72,000,000 of them have received one or more doses of vaccine, leaving about 37,000,000 Americans under 40 who have not received vaccine. Only 28,000,000 persons are estimated to have received the full course of three properly spaced shots of vaccine. The chronology and distribution of this vaccine is shown in Table 3.

When vaccine was scarce, in 1955, its use was concentrated on the 5- to 9-year age group, with highest incidence of poliomyelitis. Its use was expanded to include all children under 20 in 1956, and vaccine was urged for all people under 40 in 1957. At the approach of the 1957 poliomyelitis season, therefore, the children in the intermediate age group had been exposed to vaccination for a period of three years and the majority had received two or more injections of vaccine. It is interesting and probably significant that this age group (5 to 14) experienced the lowest paralytic rates in 1957, as shown in Table 1.

Influence of Vaccination

The frequency of paralysis among vaccinated children in 1956 was estimated to be about 75% less than in unvaccinated children.[3,6] This trend is noted again in 1957, with up to 90% protection in triple-vaccinated children. These figures are estimates, because there are no longer adequate numbers of unvaccinated children for controls. The crude preliminary data from 39 states show that only 21% of diagnosed cases among vaccinated patients were paralytic,

TABLE 4.—*Vaccinated Poliomyelitis Cases by Age, Paralytic Status, and Number of Inoculations* *

Age Group	1 Inoculation		2 Inoculations		3 Inoculations	
	Cases	% Par.	Cases	% Par.	Cases	% Par.
0–4	36	64	94	49	61	21
5–9	40	40	108	16	172	12
10–14	24	33	63	11	101	8
15–19	15	27	45	20	26	23
20+	41	22	85	19	26	19
All	156	39	395	24	386	14

* Preliminary data from 39 states and territories, January to August, 1947, P. S. U. Report, No. 133, Nov. 1, 1957 (excluding 212 cases with number of doses unknown).

while 50% were paralytic among nonvaccinated patients. This lower frequency of paralysis among vaccinated than among nonvaccinated is apparent in each age group and in every analysis made over the past four years. When the 1957 cases [5] among vaccinated persons are tabulated according to number of vaccine injections received it is apparent (Table 4) that the percentage with paralysis decreases from 39% for those who had received one injection to 24% for those who had received two injections to 14% for patients who had received three or more injections. These results may change with further analysis, since 212 cases were excluded because the number of injections of vaccine was unknown.

Triple-Vaccinated Cases

Through October the Poliomyelitis Surveillance Unit of the Public Health Service received reports of 97 paralytic cases, including 1 fatal case, and 427 nonparalytic cases in 28,000,000 persons who had received three doses of poliomyelitis vaccine. Eighteen per cent of these cases were paralytic, but careful analysis and follow-up may show that the diagnosis cannot be confirmed in many. In 1956 there was only one fatal case in a triple-vaccinated child [6] and of 19 confirmed paralytic cases in triple-vaccinated children poliovirus was isolated from only 7.

Safety of Vaccine

After May, 1955, a series of modifications in the requirements for making an acceptable poliomyelitis vaccine was instituted by the Technical Committee on Poliomyelitis Vaccine of the Public Health Service. These modifications were the result of extensive investigation and experience by the Committee, the manufacturers, and other research workers. The chief changes were requirements for (1) filtration through a Seitz bacterial filter just before addition of formaldehyde, (2) repeat filtration through a Seitz pad during the formaldehyde inactivation process, (3) two negative tissue-culture safety tests of 500 ml. each on monovalent pools during the inactivation process, (4) a negative tissue-culture safety test on a 1500 ml. sample of the trivalent pool, (5) a monkey safety test of not less than 230 ml. injected intramuscularly and intracerebrally into monkeys pretreated with cortisone, and (6) no change in the potency requirements of acceptable vaccine as measured by stimulation of antibody production in vaccinated monkeys. In addition, all manufacturers increased the formaldehyde inactivation time and added other measures which experience had shown to be useful. The result of these combined safeguards has been a completely safe vaccine as judged by the safety tests and confirmed beyond question by injection into millions of children. In 1956 there were 70,000,000 injections given, many of them during the poliomyelitis season or in epidemic areas. In these vaccinees, 500 cases of poliomyelitis occurred within 30 days after injection, of which 229 were paralytic, or 1 case per 300,000 vaccine injections. The criteria [3] for suspecting that poliomyelitis is associated with vaccine injection are as follows: (*a*) frequency of association between use of certain lots of vaccine and occurrence of poliomyelitis, (*b*) concentration of cases in the period between 4 and 14 days after injection, and (*c*) correlation between the site of injection and the site of first paralysis. During 1957 over 80,000,000 doses have been used by estimate and there has

been no evidence of live virus in the vaccine as judged by the criteria listed above.

Vaccination Under Epidemic Conditions

The trauma of an injection administered in the midst of an epidemic of poliomyelitis in a person undergoing an asymptomatic infection might possibly precipitate paralysis by some mechanism similar to that following injection of diphtheria and pertussis depot antigens. The routine surveillance studies have provided evidence against this, and two large epidemics carefully studied in 1955 and 1956 provided confirmatory information.

Among the U. S. Naval personnel and dependents during an epidemic in Hawaii in 1957,[7] there were 25,000 persons vaccinated, with no evidence of a provoking effect. In the Chicago epidemic of 1956, there were 1,770,000 doses of vaccine given,[8] with no evidence that paralysis was increased in the limb injected.

In addition, these two studies indicate that emergency vaccination cannot be expected to alter the course of an epidemic. In Chicago the epidemic continued for two months after vaccination was started, and in Hawaii the epidemic stopped four weeks after mass vaccination. In the Hawaii study γ-globulin was given to 1518 of the 1830 adults and children in the housing project where the epidemic began and where 9 of the first 14 cases had occurred. In the γ-globulin-treated group only one nonparalytic case developed symptoms three days after receiving γ-globulin. In contrast, cases continued to occur in persons given vaccine. This supports the conclusion of Muench[9] that γ-globulin was 50% effective in epidemic areas in 1953 and indicates that γ-globulin and not vaccine should be used if epidemic outbreaks continue or recur.

Potency of Vaccine

Potency of vaccine can be estimated by three methods as follows: laobratory tests in animals or test tubes, antibody response in man, and, finally, large-scale vaccination programs to note the effect on naturally occurring poliomyelitis in man. Vaccines prepared by the present methods are in general not as potent by laboratory assay as some of the early commercial lots,[2] but all vaccines released must still meet the same potency requirements, established in April, 1955. Some of our previously unreported data are typical of the antibody response in man. In 33 children with no detectable antibody for any type of virus one injection of vaccine was given, followed by a second injection 7 months later and a third injection 13 months later. Blood samples were drawn before and after each injection and analyzed for antibody against 100 $TCID_{50}$ of each virus type. It is obvious (Table 5) that these children responded poorly to a single dose of vaccine, and even three doses did not elicit a good titer of Type 1 and Type 3 antibody in every child. Since Type 1 virus causes most paralytic poliomyelitis, it would seem logical to fortify the vaccine with Type 1 antigen at the expense of the Type 2 component.

Others have noted poor antibody response in triple-negative children when compared with children with prevaccination detectable antibody against one or more types. Type

TABLE 5.—*Antibody Responses of Triple-Negative Children Following Three Successive Injections of Poliomyelitis Vaccine at Intervals of Six to Seven Months*

Vaccine				Antibody Present					
Date	Lot No.	Patients, No.	Titer	Type 1		Type 2		Type 3	
				No.	%	No.	%	No.	%
4/55	236	34	> 4	2	6	21	68	1	3
			>16	0	0	2	6	1	3
11/55	240	34	> 4	26	76	34	100	16	20
			>16	21	62	32	94	3	9
5/56	250	28	> 4	28	100	28	100	21	75
			>16	26	92	28	100	15	54

2 virus appears to be the best antigen, and Types 1 and 3 are less effective. In spite of this, the field record of the Salk vaccine suggests 75% to 80% protection, and in children who have had the full course of three shots the protection approaches 90%. It would appear logical that a fourth dose of the present vaccine would establish immunity in an even larger percentage of persons.

Duration of Protection

Duration of protection can only be surmised from the persistence of detectable antibody in the blood for a period of one or two years [10,11] in some patients and up to three and one-half years in others plus the heightened reactivity to reinjection of vaccine which seems to persist for an undetermined period even after antibody can no longer be measured. At the moment there are not sufficient data to predict how long immunity lasts after vaccination,[12] and until more information is accumulated this question had best be left unanswered. If poliomyelitis vaccine is marketed in combination with pertussis-diphtheria-tetanus antigens and booster shots are given along with the latter three antigens, the question of duration of immunity would be handled in a manner which has proved useful with other antigens.

Early Objections to Killed Vaccine

Some criticisms of a killed as opposed to a living poliomyelitis vaccine which received serious consideration in the early days of the use of the Salk vaccine were reviewed by Stanley.[17] After four years of experience with a killed poliomyelitis vaccination it might be well to restate these problems, which were the following:

(1) Chemical irritation of tissues by the vaccine

(2) Sensitization to kidney protein, penicillin, or allergic encephalitis

(3) Sensitization to Rh antigens

(4) Production of malignant tumors at the injection site

(5) Preparation of sufficient quantities of killed vaccine to immunize millions of people

(6) Difficulty in evaluating the safety of a killed vaccine as compared with a living vaccine

(7) Possibly slow and laborious evaluation of effectiveness

All of these potential problems have been resolved or have not developed. Safety was a serious problem, and this did not become apparent during the 1954 field trial. Evaluation of the effectiveness of the killed vaccine has indeed been slow, and at least one more year of field experience and research will be necessary before a final answer can be given.

Added Knowledge

Other contributions of the poliomyelitis vaccine program are landmarks in the progress of disease control: It is (1) the first vaccine produced in tissue culture on a mass scale, (2) the first human vaccine produced in a primate cell, and (3) the first large-scale production of virus containing very little foreign protein; (4) the technical and control methods for mass production of tissue cultures have been perfected in industry; (5) safety testing and control of virus vaccines have developed to a science, and a new department of the National Institutes of Health has been developed to carry out these functions; (6) control procedures developed for licensing poliovaccine will undoubtedly apply in some form to other vaccines developed from tissue cultures in the future.

Problems Created by the Vaccine

Supply, Demand, Distribution, and Black Market.—1. Poliomyelitis vaccine is the first vaccine released by the Public Health Service directly to the state departments of health and commercial channels, accompanied by press, radio, and television campaigns urging its use. These processes created a large demand for vaccine which was accentuated by manufacturers' failure to meet production estimates. The resultant

shortage of vaccine created many problems which could possibly be avoided. This same sequence was repeated again with the recent Asian influenza vaccine program. A possible lesson to be learned here is that the American public will immediately accept a new medication which is endorsed by the Public Health Service. The pace of recent advances in biological research will undoubtedly bring new preventive measures in the future, and all organizations concerned with medical care should develop plans for meeting distribution problems like those presented by the Salk vaccine.

2. Shortage of monkeys may become a problem when the vaccine is used on a world-wide basis, and this has led to an intensive and so far unsuccessful search for another tissue which can be used for producing the vaccine.

Reactions.—Unfavorable reactions to poliomyelitis vaccine have been remarkably few and are less than with any other vaccine in current use. There have been no reports of nephritis or renal disease following vaccination or hematological reactions to Rh or other blood factors. Local and generalized allergic reactions have occurred rarely. Urticaria has been observed, particularly in persons known to be hypersensitive to penicillin.[18] In 1956 there were reported following vaccination two cases of encephalitis, five cases of myelitis, one sudden death, and a few cases of meningismus, febrile convulsions, and labyrinthitis. The small number of such reactions among the 70,000,000 persons vaccinated makes it very unlikely that there was any specific causal relationship between vaccination and the observed illnesses. However harmless polio-vaccine now appears to be, final judgment should be reserved, because each new medication introduced into clinical practice is likely to be free from reports of unfavorable reactions at first, and a true evaluation is only possible after the passage of time, more extensive use, and an opportunity for delayed reporting of observations. There are no reports of unusual untoward reactions to vaccination in 1957, and presumably these have followed the same pattern as in 1956.

Aseptic Meningitis

Within the last few years at least 66 new viruses have been isolated and identified, many of which are capable of causing symptoms resembling nonparalytic or paralytic poliomyelitis. Kumm[22] has reviewed many localized summer epidemics of aseptic meningitis reported since 1953 which were associated with Coxsackie or ECHO viruses. An extensive epidemic of aseptic meningitis in Belgium in 1956[19,20] associated with a skin rash was caused by ECHO Type 9 virus. Similar cases have been observed in this country in 1956, and in 1957 Sabin[21] showed that summer outbreaks in Milwaukee and Cincinnati were caused by ECHO virus Type 9. Many other outbreaks without rash have been recognized in the United States in 1957, and their etiology is still being investigated. From the data already reported and documented it seems clear that at least 17 viruses which were unknown 10 years ago may cause symptoms in man which are indistinguishable from poliomyelitis except by laboratory tests. Paralysis is rare, but at least 12 of these viruses have been associated with mild or transitory paralytic disease, and when these are added to the nonpoliomyelitis viruses which were already known to simulate poliomyelitis (Table 6) it becomes clear that the diagnosis of either paralytic or nonparalytic poliomyelitis cannot be confirmed on the basis of clinical

TABLE 6.—*Viruses Which Must Be Considered in the Laboratory Diagnosis of Poliomyelitis*

Name	No. of Strains Known	Strains Causing CNS Disease	
		Nonparalytic	Paralytic
Poliovirus	3	1, 2, 3	1, 2, 3
ECHO virus	19	4, 5, 6, 7, 9, 14, 16	4, 6, 7, 10
Coxsackie A	10	1, 4, 7, 8, 9, 10	1, 4, 7, 8, 9, 10
Coxsackie B	5	2, 3, 4, 5	3, 4
Equine encephalitis	3	3	2
Herpes simplex	1	1	1
Herpes zoster	1	1	1
L. C. M.	1	1	1
Mumps	1	1	1
	53	25	19

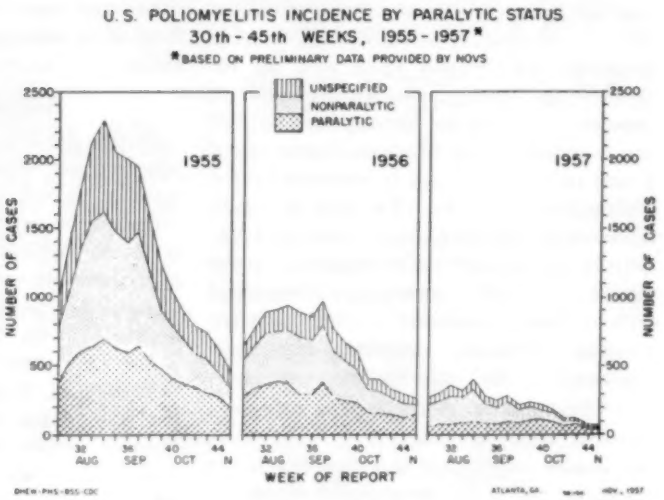


Fig. 3. — Data reproduced from Communicable Disease Center Poliomyelitis Surveillance Report No. 134, Nov. 15, 1957.

findings alone. Considering all the information available, it is probable that these new viruses are not new but are just now being recognized. Hammon [2] reported in 1957 that the untypable viruses isolated from paralytic poliomyelitis in 1952 during the γ-globulin studies in Iowa and Texas have now been identified as Coxsackie B3 and B4, Coxsackie A9, and ECHO 4, 7, and 16.

One might ask whether the dramatic decreases in reported poliomyelitis cases during the past three years are due to the effects of the Salk vaccine or to more accurate diagnosis of aseptic meningitis cases caused by other viruses. Both these explanations are probably true, but, as shown in Figure 3, the greatest reduction of poliomyelitis has been in the paralytic type rather than in the nonparalytic type. It seems probable also that some of the reported cases of paralytic poliomyelitis in vaccinated children may be actually caused by other viruses, although paralysis is comparatively rare in these other diseases.

Living Attenuated Vaccine

The chief advantage of a living attenuated oral vaccine in poliomyelitis is that it might confer permanent immunity. Antibody has been shown to persist at a constant level for up to six years following oral vaccination.[14-16] The mechanism by which permanent immunity is maintained following natural infection is not clear. It is not known, for example, whether repeated reinfections are necessary to maintain lifelong immunity. There is evidence [12-16] that vaccination with Salk vaccine does not prevent subsequent alimentary reinfection whereas oral vaccination with live virus almost always does so. It is possible, in spite of laboratory evidence to the contrary, that widespread vaccination with killed vaccine will reduce the amount of circulating poliovirus so that natural reinfection does not occur. The absolute reduction of cases in adults as well as in children in 1957 suggests that this may be taking place. Such a trend could possibly lead to virtual elimination of poliomyelitis viruses. If this occurs and if reinfection is necessary for keeping up immunity, then a susceptible population might develop within a few years unless repeated vaccination is carried out. If this proves to be necessary, a safe oral vaccine would have advantages over repeated parenteral injection of a killed vaccine. It has been assumed by most workers that the degree of attenuation desirable in an acceptable living vaccine is complete

absence of ability to produce paralytic disease following intracerebral and intraspinal injection into monkeys. Such a completely avirulent virus has not yet been developed and may not be desirable, since it might be associated with complete loss of ability to stimulate antibody formation following oral feeding to infants, as is suggested by the recent studies of Koprowski.[14-16]

Possible drawbacks to a living attenuated vaccine are that it may contain other living viruses, may regain virulance on human passage, and may also not confer permanent immunity or immunity to all strains of poliovirus. Additional research is needed to clarify these problems.

Summary and Recommendations

Three years of increasingly widespread use of killed poliomyelitis vaccine have coincided with marked reduction in reported cases of poliomyelitis. A particularly low incidence and low paralytic rate are the outstanding features of the 1957 season. Up to Nov. 15, there have been 1988 cases of paralytic poliomyelitis reported for 1957, compared with 6196 for the same period in 1956 and 9796 for 1955.

The decrease this year occurred in all age groups, with a relatively greater proportion of cases occurring in patients from birth to 4 years of age. Estimates suggest that protection against paralytic disease approached 90% in patients who had received three or more properly spaced injections of vaccine. Approximately 28,000,000 of the 109,000,000 persons under 40 years of age have received a full course of three injections of vaccine.

At least 17 strains of Coxsackie or ECHO viruses can cause a clinical disease resembling nonparalytic or occasionally paralytic poliomyelitis. These infections have almost certainly been called poliomyelitis in the past. Further research will show how many of the vaccine failures are infections caused by one of these other viruses.

The vaccine is safe, at the sacrifice of some potency. Suggestions for further research for improving potency are (1) disproportionate mixing of the three virus fluids in making the vaccine, (2) increasing the potency requirements, and (3) selection of new strains of virus. Such changes take time and will probably not be available before the next poliomyelitis season. In the meantime, we must use the vaccine which is at hand, and the immediate objective should be to complete three properly spaced injections for all persons in the susceptible age group.

The use of vaccine in two epidemics in 1955 and 1956 has not shown any beneficial effect on the course of the epidemic. This emphasizes the importance of doing vaccination ahead of the anticipated poliomyelitis season.

Living attenuated vaccines for oral immunization are still experimental, but there is laboratory evidence that oral attenuated vaccine prevents alimentary reinfection and thus the shedding of virus, while killed vaccine does not. The attenuated strains are much less virulent than the natural wild strains, and so perhaps it is unnecessary to search for completely avirulent strains. Much more knowledge and research is necessary before a live vaccine can replace the killed vaccine, but it might receive first widespread use as a booster following primary immunization with killed vaccine.

In view of the evidence reviewed in this report, it seems logical to predict that poliomyelitis will be reduced even more drastically in 1958, provided that the vaccination program is continued including a full course of three properly spaced injections for all persons under 40 years of age. Available data suggest that the present vaccine offers the possibility for virtual elimination of paralytic poliomyelitis as a significant disease in the United States in 1958, and all physicians are urged to cooperate by completing immunizations.

In my opinion and on the basis of the data now available, a fourth injection of vaccine is indicated in the spring of 1958,

just before the next poliomyelitis season. This is based on the observations that (1) although the vaccine is safe and effective, some paralytic cases continue to occur in triple-vaccinated children and (2) protection appears to be proportioned to the amount of antigen injected; (3) many children have received incomplete series, improperly spaced injections, or vaccine of poor potency, and (4) there seem to be remarkably few reactions or contraindications to the vaccine. This proposed fourth injection is viewed not as a booster but rather as a method for completion of the primary immunization of those who for one reason or another failed to develop an immunologic response to previous injections. The actual need for booster shots after this primary immunologic response has not been demonstrated and may not be necessary at all after the population is once immunized, except perhaps in infancy and early childhood. At any rate, decision on a permanent plan for future booster shots should certainly be deferred pending more research.

Camden Municipal Hospital for Contagious Disease.

REFERENCES

1. Francis, T., Jr., and others: An Evaluation of the 1954 Poliomyelitis Vaccine Trials: Summary Report, Am. J. Pub. Health 45:1-50 (May, Pt. 2) 1955.

2. Discussions presented at Fourth International Poliomyelitis Congress, Geneva, Switzerland, July, 1957.

3. Langmuir, A. D.; Nathanson, N., and Hall, W. S.: The Surveillance of Poliomyelitis in the United States in 1955, Am. J. Pub. Health 46:75-88, 1956.

4. Langmuir, A. D.; Nathanson, N.; Hall, W. S.; Thrupp, L. D., and Forester, H.: Surveillance of Poliomyelitis in the United States in 1956, Pub. Health Rep. 72:381-392, 1957.

5. Communicable Disease Center Poliomyelitis Surveillance Reports issued weekly by the U. S. Dept. of Health, Education, and Welfare, No. 133, Nov. 1, 1957; No. 134, Nov. 15, 1957.

6. Poliomyelitis, Annual Statistical Review, 1956, New York, National Foundation for Infantile Paralysis, 1956.

7. Poos, R. S., and Nathanson, N.: Use of Poliomyelitis Vaccine Under Epidemic Conditions: Report of Outbreak of Poliomyelitis Among Naval Personnel and Dependents in Hawaii, J. A. M. A. 162:85-92, 1956.

8. Bundesen, H. N.; Graning, H. M.; Goldberg, E. L., and Bauer, F. C.: Preliminary Report and Observations on the 1956 Poliomyelitis Outbreak in Chicago: With an Evaluation of the Large-Scale Use of Salk Vaccine, Particularly in the Face of a Sharply Rising Incidence, J. A. M. A. 163:1604-1619, 1957.

9. Muench, H.: Influence of Passive Immunization on the Incidence of Poliomyelitis, in Third International Poliomyelitis Conference, Philadelphia, J. B. Lippincott Company, 1955, pp. 149-158.

10. Salk, J. E.: Antigenic Potency of Poliomyelitis Vaccine, J. A. M. A. 162:1451-1459, 1956.

11. Salk, J. E.: Personal communication to the author.

12. Paul, J. R.: Indications for Vaccination Against Poliomyelitis, J. A. M. A. 162:1585-1588, 1956.

13. Sabin, A. B.: Present Status of Attenuated Live-Virus Poliomyelitis Vaccine, J. A. M. A. 162: 1589-1596, 1956.

14. Koprowski, H., and others: Immunization of Infants with Living Attenuated Poliomyelitis Virus: Laboratory Investigations of Alimentary Infection and Antibody Response in Infants Under 6 Months of Age with Congenitally Acquired Antibodies, J. A. M. A. 162:1281-1288, 1956.

15. Koprowski, H., and others: Immunization of Children by the Feeding of Living Attenuated Type I and Type II Poliomyelitis Virus and the Intramuscular Injection of Immune Serum Globulin, Am. J. M. Sc. 232:378-388, 1956.

16. Koprowski, H.: Personal communication to the author, 1957.

17. Stanley, N. F.: Poliomyelitis: The Experimental Approach to Its Prevention, M. J. Australia 2:417-422, 1954.

18. Bierly, M. Z., Jr.: Considerations of Special Interest to the Allergist on the Composition and Production of Poliomyelitis Vaccine, Ann. Allergy 14:349-358, 1956.

19. Nihoul, E.; Quersin-Thiry, L., and Weynants, A.: Echo Virus Type 9 as the Agent Responsible for an Important Outbreak of Aseptic Meningitis in Belgium, Am. J. Hyg. 66:102-118, 1957.

20. Quersin-Thiry, L.; Nihoul, E., and Dekking, F.: Echo Virus Type 9 (New Member of Coxsackie Group Type A?) as a Cause of Epidemic Meningitis, Science 125:744-745, 1957.

21. Sabin, A.: Personal communication to the author.

22. Kumm, H. W.: The Echo and Coxsackie Viruses and Their Relationship to Paralytic and Nonparalytic Poliomyelitis, Journal-Lancet, to be published.

Failure of Penicillin and Sulfonamide to Prevent Beta-Hemolytic Streptococcal Infections

Sibling Prophylaxis of Streptococcal Infection

BURTIS B. BREESE, M.D., and F. A. DISNEY, M.D., Rochester, N. Y.

Introduction

One of the problems that confronts the practitioner who sees a child with a streptococcal infection is whether to use chemical or antiobiotic prophylaxis on other members of the family. This study was designed to give information on the advisability of such prophylaxis. To our knowledge, there has been no published information on this subject, although Cannon [1] reported a marked effect on prevention of streptococcal infection by the use of 250,000 units of penicillin G orally once daily for five days. In 107 contacts given prophylaxis only 1 case of streptococcal infection developed, whereas in 83 contacts given no prophylaxis, 25 cases were observed. This study was done in Cooperstown, N. Y., in 1955-1956.

Material and Methods

A previous study of ours [2] showed that, although approximately 25% of family contacts of patients with primary streptococcal disease became infected, the attack rate in infants, older siblings, and adults was very low. For this reason, it was decided to limit the study to siblings from 1 year through 14 years of age. Inasmuch as the primary case, when adequately treated, becomes noninfectious in a matter of hours, it was believed that the period of prophylaxis could therefore be relatively short. It was also decided that drugs and daily dosages which had been recommended for prevention of streptococcal infection in rheumatic fever patients [3] should be used, although it was recognized that in children already infected the dosage might need to approximate that used therapeutically.

Submitted for publication Nov. 24, 1957.

From the Department of Pediatrics of the University of Rochester School of Medicine and Dentistry. Clinical Associate Professor of Pediatrics (Dr. Breese) and Assistant Professor of Pediatrics (Dr. Disney).

Three schedules were used: (1) one benzathine penicillin G tablet (200,000 units) daily; (2) one 0.5 gm. tablet of sulfadiazine daily; (3) one 0.5 gm. placebo tablet daily. Each was given for five days. All siblings in the same family received the same prophylaxis. Which schedule was used was determined by drawing at random a previously marked card from a shuffled deck of such cards containing an equal number of each of the three types of cards.

All "primary" cases were bacteriologically proven streptococcal infections seen in our private practice in Rochester, N. Y., during the winter and spring of 1953-1954. The "contacts" were siblings in the same family. In the series there were 257 primary cases and 430 sibling contacts.

When the primary case was first examined, treatment was instituted immediately if, on clinical grounds, there was a reasonable belief that the child had a streptococcal infection. Otherwise, treatment was delayed until the result of the culture, taken on all suspected cases, was known, on the following day. In almost all patients treatment consisted of a single intramuscular injection of 600,000 units of benzathine penicillin G (Bicillin). Whenever possible, a throat culture was obtained on all contacts prior to the use of prophylaxis. The parents were instructed to inform us of any illness on the part of these children. Approximately 10 days later, or five days after the completion of prophylaxis, the family was visited by our bacteriologist, who took cultures on the primary case and all sibling contacts.

Three weeks after initial therapy the primary case was reexamined and a throat culture was obtained. The mother was questioned about illness in the other siblings, and in a minority of these contacts cultures were obtained at that time. In addition, if illness in the contacts occurred at other times they were usually examined by one of us and a throat culture was obtained.

No contact was included in the study unless at least one culture was taken subsequent to prophylaxis. The one exception to this rule was the sibling whose culture was positive prior to prophylaxis.

TABLE 1.—*The Distribution of Primary Cases of Streptococcal Disease and Their Sibling Contacts According to Family Size in Relation to Type of Prophylaxis*

Siblings, No.	Benzathine Penicillin		Sulfadiazine		Placebo	
	Primary Cases (Families), No.	Contacts, No.	Primary Cases (Families), No.	Contacts, No.	Primary Cases, No.	Contacts, No.
1	59	59	44	44	47	46
2	17	34	26	52	17	36
3	15	45	9	27	8	24
4	3	12	7	28	1	4
5	0	0	3	15	1	5
Total	94	150	89	166	74	115

Almost all strains were isolated in pure culture and grouped and typed in the Streptococcus Laboratory under the direction of Dr. Elaine Updyke, at the Communicable Disease Center, U. S. Public Health Service, Chamblee, Ga.

Results

Although to our knowledge the families selected to receive each of the three types of prophylaxis were randomly selected, a smaller number received the placebo than received the other two types (Table 1). Although this difference is unlikely to be due to chance ($P=0.05$), we have no other explanation. Moreover, we were unable to demonstrate any difference in other respects in the three groups between the primary cases and the contacts.

Among the primary cases in each group the following factors showed no significant differences: size of family group (Table 1), age (Table 2), distribution of types of streptococci (Table 3), per cent of strongly positive cultures, per cent treated with benzathine penicillin, and per cent treated before 48 hours (Table 4). Moreover, among the contacts in each group no difference could be demonstrated in the size of family group (Table 1) or age (Table 2).

TABLE 2.—*Percentage in Each Age Group of Primary Cases and Contacts of Primary Cases in Each of Three Prophylactic Groups*

Age, Yr.	Per Cent of Cases in Each Age Group					
	Benzathine Penicillin		Sulfadiazine		Placebo	
	Primary (94)*	Contact (150)	Primary (89)	Contact (166)	Primary (74)	Contact (114)
0–3	11.7	30.6	6.7	28.4	6.8	31.6
4–6	44.6	28.7	40.5	29.4	55.4	27.2
7–9	32.0	19.4	37.1	19.9	23.0	21.0
10–12	10.6	17.3	13.5	18.1	14.8	14.9
Over 12	1.1	4.0	2.2	4.2	0.0	5.3
	100.0	100.0	100.0	100.0	100.0	100.0

* The number of cases in each group is given in parentheses.

TABLE 3.—*The Distribution of Types of Group A Streptococci Found in the Primary Case in Relation to Type of Prophylaxis Given Siblings*

Type of Group A Streptococci	Benzathine Penicillin		Sulfadiazine		Placebo		Total	
	No.	%	No.	%	No.	%	No.	%
A1	22	23.3	16	18.0	16	21.6	54	21.0
A3			3	3.4			3	1.2
A4			1	1.1	1	1.3	2	0.8
A5	1	1.1	2	2.2			3	1.2
A6	9	9.6	7	7.9	4	5.4	21	7.8
A12	4	4.3	2	2.2	5	6.8	11	4.2
A19	1	1.1	2	2.2	3	4.1	6	2.3
A28	4	4.3	2	2.2	1	1.3	7	2.7
ANT *	49	52.0	47	52.9	34	46.0	130	50.6
Not typed	4	4.3	7	7.9	10	13.5	21	8.2
Total	94	100.0	89	100.0	74	100.0	257	100.0

* Group A but not typable.

TABLE 4.—*Certain Attributes of the Primary Cases in Each Treatment Group* *

Prophylaxis	Contacts, No.	Primary Cases, No.	% with Strongly Pos. Culture	% Treated with Benzathine Penicillin	% Treated Before 48 Hr.
Benzathine penicillin	150	94	79	98	75
Sulfadiazine	166	89	81	93	71
Placebo	114	74	79	97	77
Total	430	257	80	97	74

* Calculations based on I. B. M. cards of contacts.

One hundred ninety-six contacts were cultured prior to prophylaxis, and two hundred thirty-four were not cultured. Of those cultured originally, 45 were found to be positive and were excluded from further study (Table 5). Of those cultured originally and found to be negative (151), 15 were subsequently found to have positive cultures and 10 of these were ill (Table 6). In 9 of the 15 it was possible to compare the type of Streptococcus found in the primary case and in the contact case. In only one case was it the same. Thus, with the small numbers involved, no statistically significant difference could be demonstrated in the attack rate of streptococcal infection between the various prophylactic groups.

TABLE 5.—*Cultures Positive for Hemolytic Streptococci Taken from Contacts Prior to Prophylaxis*

Prophylaxis Group	Contacts Cultured, No.	Cultures Positive for Hemolytic Streptococci	
		No.	Per Cent
Benzathine penicillin	75	18	24.0
Sulfadiazine	58	11	19.0
Placebo	63	16	25.4
Total	196	45 *	23.0

* Eight cases ill. In 25 cases it was possible to compare the type of Streptococcus found in primary and in the contact case. In 14, or 56%, the types were the same.

TABLE 6.—*Contacts with Negative Cultures for Hemolytic Streptococcus Prior to Prophylaxis Whose Cultures Became Positive in Follow-Up Period*

Prophylaxis Group	Contacts Cultured, No.	Cultures Positive for Hemolytic Streptococci in Follow-Up Period	
		No.	Per Cent
Benzathine penicillin	57	4	7.0
Sulfadiazine	47	7	14.9
Placebo	47	4	8.5
Total	151	15 *	9.9

* Ten cases ill. In nine cases it was possible to compare the type of Streptococcus found in the primary case and in the contact. In only one case were the types the same.

Among the 234 contacts not cultured originally, subsequently 35 cases were found to be positive and 11 of these were ill. In these contacts, also, no statistically significant difference could be demonstrated in the frequency of streptococcal infections in those given different prophylactic schedules (Table 7). In five cases it was possible to compare the type of Streptococcus found in the primary case and the contact. In only one instance was the type the same.

TABLE 7.—*Contacts Not Cultured Originally Whose Cultures Were Subsequently Found to Be Positive for Hemolytic Streptococci*

Prophylaxis Group	Contacts Cultured, No.	Cultures Positive for Hemolytic Streptococci	
		No.	%± Standard Error
Benzathine penicillin	75	8	10.7±3.6
Sulfadiazine	108	19	17.6±3.7
Placebo	51	8	15.7±5.1
Total	234	35 *	15.0

* Eleven cases ill. In five cases it was possible to compare the type of Streptococcus found in the primary case and in the contact. In only one were the types the same.

Thus from these data, under the conditions of the experiment, involving a single series of observations in one community and only small doses of prophylactic agents, it would appear that little is to be gained by prophylaxis of siblings of children with primary streptococcal infections. Moreover, this series of observations would seem to indicate that probably a high proportion of infections in siblings occur before prophylaxis can be given to them.

Comment

The conclusion reached from our observations should not be construed to indicate that prophylaxis with penicillin and sulfadiazine is generally ineffectual against strep-

tococcal infection. This certainly is not true. One of us (B. B.) took part in the very effective sulfadiazine prophylactic program of the Navy in its training camps during World War II.[4] That this program later failed because of the appearance of sulfadiazine-resistant strains of β-hemolytic streptococci [5] does not alter the fact that the sulfonamides are excellent agents for individual prophylaxis against the majority of streptococcal infections. In a controlled study during the war [6] it was found that 0.5 gm. of sulfadiazine daily was as effectual as 1.0 gm. in adults. Moreover, other studies in rheumatic fever patients have indicated that these drugs are effective.[7-9] Similarly, Seal's recent studies [10] on Navy recruits have shown that penicillin given in a dosage of as little as 50,000 units daily is effective in preventing streptococcal infection. Markowitz has shown that benzathine penicillin G given in a single dose of 200,000 units daily in patients with rheumatic fever is effective in preventing streptococcal infection.[11] In the last-mentioned series sulfadiazine was also found to be effective. Other data have been accumulated to confirm these findings with varying dosage schedules. Two of the earliest of these observations were reported by Massell et al.[12] and by Kohn and his co-workers.[13]

The problem of prophylaxis of siblings of a child who has what appears to be an initial streptococcal infection is another matter. In the first place, as shown in this and our previous study,[2] the sibling is frequently infected before prophylaxis can be administered. In the second place, if he has not been infected by the time the primary case is first seen, he is not very likely to be infected subsequently from the same source, since the primary child's illness rapidly becomes noninfectious under the impact of penicillin therapy. While the rheumatic child is given continuous prophylaxis, contacts of streptococcal illness, from the practical standpoint, can be given penicillin prophylaxis only for a limited time. Essentially what one is dealing with in the sibling contact is a child who has already had an unrecognized and untreated streptococcal infection or who is already incubating it. After a matter of hours he has little to fear from the treated child. At best, therefore, our prophylaxis must be aimed at suppressing and eliminating an infection which is in its incipient stages or protecting him against other unrecognized sources of infection within the household. If he has had an unrecognized infection in the recent past we are faced not with prophylaxis but with the problem of treating a carrier. We have found, as have others, that carriers require full or nearly full therapeutic doses of penicillin to eliminate the organism.[10] It is obvious that if full therapy is given to all children in the same family, streptococcal disease will be eliminated in all, but prophylaxis should certainly be less than therapy.

Admittedly, our dosage schedule is not great, nor is its duration long. Other dosage schedules might be more effective and still be less rigorous than full therapeutic regimen. Nonetheless, our studies seem to indicate that the field for prophylaxis is limited. Our feeling would be that it is wiser to watch for illness in the siblings and then give full therapeutic dosage. As for carriers or unrecognized cases in the family, unless cultures are taken these will be missed in many cases. Simple questioning will often, however, elicit the story of a mild "sore throat" in another member of the family (usually an older brother or sister). In the absence of a culture this child should be at least suspected of being a carrier. Prophylaxis is not for him; therapy is needed to eliminate the Streptococcus.

Moreover, it is probable that prophylaxis may give a false sense of security, may obscure rather than cure an early infection, and may create more problems than it prevents. Therefore, we do not recommend it in sibling contacts of children with streptococcal disease.

Summary and Conclusions

The siblings of 257 children suffering from streptococcal infection were given prophylaxis with benzathine penicillin G, sulfadiazine, or a placebo. These siblings were examined bacteriologically and, if ill, clinically also after the prophylaxis.

There was no essential difference in the attack rate of secondary streptococcal infections in the three prophylactic groups.

It is concluded that prophylaxis for siblings as given was of no value in preventing infection, and it is therefore not recommended.

The reasons for failure of prophylaxis of siblings of primary cases of streptococcal disease are discussed in contrast with the excellent results of prophylaxis in rheumatic patients and military groups given continuous prophylaxis with either the sulfonamides or penicillin preparations.

This study was supported by a grant from Wyeth Laboratories, Inc. The Rochester Health Bureau supplied the media used in this study.

Mrs. Clinton Wolcott and Miss Noreen Ireland gave technical assistance in the carrying out of this study.

Advice on statistical methods used was given by Dr. S. Lee Crump.

2333 Elmwood Ave. (18).

REFERENCES

1. Cannon, J. H.: Report read before Central New York Pediatric Club, May 24, 1956.

2. Breese, B. B., and Disney, F. A.: The Spread of Streptococcal Infections in Family Groups, Pediatrics 17:834, 1956.

3. Committee on Prevention of Rheumatic Fever, American Heart Association: The Prevention of Rheumatic Fever and Bacterial Endocarditis Through Control of Streptococcal Infections, Circulation 15:154, 1957.

4. The Prevention of Respiratory Tract Bacterial Infections by Sulfadiazine in the United States Navy, Epidemiology Unit No. 22, NAVMED 284, Bureau of Medicine and Surgery, Navy Department, Washington, D. C., U. S. Government Printing Office, 1944.

5. Epidemiology Unit Number 22: Sulfadiazine Resistant Strains of Beta Hemolytic Streptococci: Appearance During the Course of Sulfadiazine Prophylaxis at a Large Naval Training Center, J. A. M. A. 129:921, 1945.

6. Epidemiology Unit Number 22: Unpublished Report to Bureau of Medicine and Surgery, Department of the Navy, 1944.

7. Coburn, A. F., and Moore, L. V.: The Prophylactic Use of Sulfanilamide in Streptococcal Respiratory Infections with Special Reference to Rheumatic Fever, J. Clin. Invest. 18:145, 1939.

8. Kuttner, A. G., and Reyersbach, G.: The Prevention of Streptococcal Upper Respiratory Infection and Rheumatic Recurrences in Rheumatic Children by the Prophylactic Use of Sulfanilamides, J. Clin. Invest. 22:77, 1943.

9. Baldwin, J. S.: Sulfadiazine Prophylaxis in Children and Adolescents with Inactive Rheumatic Fever, J. Pediatrics 30:288, 1947.

10. Seal, J. R.: Oral Penicillin Prophylaxis of Streptococcal Infections, Am. J. Pub. Health 45: 662, 1955.

11. Markowitz, M., and Hemphill, W.: A Comparison of Oral N,N'-Dibenzylethenediamine Dipenicillin G and Sulfonamides for the Prevention of Streptococcal Infections and Recurrences of Rheumatic Fever, in Antibiotics Annual 1954-1955, New York, Medical Encyclopedia, Inc., 1955, p. 83.

12. Massell, B. F.; Dow, J. W., and Jones, T. D.: Orally Administered Penicillin in Patients with Rheumatic Fever, J. A. M. A. 138:1030, 1948.

13. Kohn, K. H.; Milzer, A., and MacLean, H.: Oral Penicillin Prophylaxis of Recurrences of Rheumatic Fever: Interim Report on Method After a 3-Year Study, J. A. M. A. 142:20, 1950.

Addison's Disease in Three Six-Year-Old Boys

BERNARD MATHIS MALLOY, M.D., and CALVIN W. WOODRUFF, M.D., Nashville, Tenn.

Addison's disease is rare in childhood. In reviewing the literature prior to June, 1945, Jaudon [1] found 12 cases in children aged 10 years or less. Since that time only 12 cases have been reported in the available literature.[2-11] Cases of adrenal failure associated with the adrenogenital syndrome were excluded, as were cases occurring before the age of 2 years, because these appear to be a separate group of patients.[12] Among these 12 cases reported, 5 were associated with hypoparathyroidism or moniliasis or had a sibling with this combination of diseases.[8-11] Four of these five occurred in two families in which other cases of "the syndrome of familial juvenile hypoadrenocorticism and superficial moniliasis" [13] occurred. In none of these cases associated with hypoparathyroidism and/or moniliasis was tuberculous involvement of the adrenal found. Tuberculosis is becoming an unusual cause of Addison's disease in childhood, as it has become in adults, being found in none of the 12 cases in children 10 years of age or younger reported since 1945.

Three 6-year-old boys having Addison's disease were admitted to the pediatric wards of Vanderbilt University Hospital between September, 1954, and October, 1955. The first case also had hypoparathyroidism and moniliasis. Observations on erythrocyte sodium and potassium concentrations were made during the initial treatment of this case.

Received for publication Oct. 2, 1957; accepted Nov. 4.

From the Department of Pediatrics, School of Medicine, Vanderbilt University. Present address: Payne Whitney Psychiatric Clinic, 525 E. 68th St., New York (Dr. Malloy); Markle Scholar in Medical Science (Dr. Woodruff).

Report of a Case

CASE 1.—A 6-year-old white boy was first admitted on Sept. 3, 1954, with the chief complaint of vomiting.* No significant family history was obtained. He had had an episode of vomiting at 1 year of age and an unknown number of poorly described "convulsions" at intervals of about two weeks between 1 and 3 years of age. Growth and development were within normal limits. Little attention was given to the striking suntan he had acquired in the preceding five months, since the maternal relatives were swarthy. Six weeks prior to admission anorexia, lethargy, vomiting, nocturia, and polyuria were noted. Three weeks later many small black spots appeared in the skin. Six days before admission pernicious vomiting, weakness, and severe thirst appeared. He complained of a sore mouth. On physical examination, the oral temperature was 100.8 F; pulse rate, 108; respiration rate, 30; blood pressure, 68/30, and weight, 36 lb. He was an acutely and chronically ill white boy who was rational but in obvious distress. The skin, including the palms, soles, and perianal and genital areas, was dark brown, with accentuation of the pigmentation over the elbows, knees, and ankles. Brownish-black areas 1 to 3 mm. in diameter were widely scattered over the body; other pigmented areas over the trunk and extremities, presumably the sites of insect bites, were noted. No cataracts were seen. The nails were not remarkable. The angles of the mouth were slightly cracked. The lips were magenta, with shiny irregular blue-black, pigmented areas at the subcutaneous junction. The tongue was smooth and beefy-red. The heart, lungs, and abdomen were within normal limits. The genitalia were of normal size and configuration. The laboratory determinations are summarized in Table 1. An admission electrocardiogram was within normal limits except for sinus tachycardia. A calcified primary complex was noted on roentgenologic chest examination. No calcification of the adrenal glands was seen on roentgenologic examination. Tuberculin and histoplasmin skin tests were negative. The histoplasmin complement-fixation test was postive at 1:10 dilution and negative at 1:20 dilution.

* This patient was referred by Dr. James C. Overall.

TABLE 1.—*Laboratory Data in Case 1*

	9/3/54	10/7/54	4/28/55	6/4/55	7/1/55	8/26/55	9/29/55	11/18/55
NPN, mg./100 cc.	75		32		39	28	42	23
Na, mEq./L.	124.8	135.2	130.0	135	132.5	132.5	123.7	133.5
Cl, mEq./L.	83.4	93.9	88.8	84.6	91.1	89.4	84.6	91.5
K, mEq./L.	6.0	5.5	4.9	3.9	4.0	5.1	4.7	4.8
CO_2, mEq./L.	16.4		21.7		25.0	19.2	24.2	20.5
TSP, Gm./100 cc.	8.0		7.3		7.3	8.0	9.4	8.8
Albumin, gm./100 cc.			4.5		4.5	4.9	5.2	4.8
Ca, mg./100 cc.		7.8	6.6	5.8	9.5	7.0	6.3	7.5
P, mg./100 cc.		9.4	9.8	10.0	5.8	9.0	8.7	7.7
Sugar, mg./100 cc.				95	81			
Hgb., gm./100 cc.	11.9		11.8	11.0	8.0	10.8	11	9.7
Total eos./cu. mm.	1,125	813	1,009		194		66	
Wt., lb.	36	43	45¼	48	50½	49½	47	47

TABLE 2.—*Balance Data for Case 1*

Time, Hr.	Fluid, Ml.		Sodium, mEq.		Chloride, mEq.		Potassium, mEq.	
	Intake	Output	Intake	Output	Intake	Output	Intake	Output
0–4	525	116	84.0	4.3	77.0	2.8	0.0	1.8
4–15	1125	991	176.4	41.0	169.4	31.4	0.0	11.2
Total		+659		+215.1		+213.2		−13.0

TABLE 3.—*Plasma Values During Initial Observation of Case 1*

Sample	Time, Hr.	Het., %	pH	pCO_2 Mm. Hg	HCO_3 mEq./L.	CO_2 Content, mEq./L.	H_2O, %	Na, mEq./L.	Cl, mEq./L.	K, mEq./L.
1	Adm.	37	7.38	36.90	16.25	19.05	93.3	124.3	83.4	6.0
2	41	28	7.50	29.81	23.45	25.05	94.2	134.8	96.2	4.1
3	113	31	7.44	35.55	24.48	21.90	93.5	135.9	100.3	4.7
4	161	29			23.22		93.2	132.6	101.3	5.3

The patient was given 150 mg. of cortisone intramuscularly and an intravenous infusion containing 50 mg. of hydrocortisone in 5% dextrose in saline. By the fourth hour his blood pressure had increased to 90/60 and he was afebrile, hungry, and less restless. Sodium, chloride, potassium, and water balances were calculated for the first 15 hours of treatment and are presented in Table 2. A study of changes in the erythrocyte cation and water concentration was performed by one of us (B. M. M.). The results are presented in Tables 3 and 4. On the third hospital day administration of intravenous fluids was discontinued and he was given cortisone, 50 mg., and sodium chloride, 12 gm., daily by mouth in addition to a normal diet. He was discharged on the seventh hospital day, taking cortisone, 25 mg., and sodium chloride, 12 gm., orally each day. He had gained 2½ lb. since admission.

After discharge the skin pigmentation gradually regressed and the patient's appetite remained good. He gained 10 lb. in three months. At that time maintenance therapy was changed to hydrocortisone by mouth, 10 mg. daily. The angular fissuring and the glossitis remained. A white fibrous exudate was noted on the tongue six months after the first admission. Although the histoplasmin and tuberculin skin tests remained negative, the histoplasmin complement-fixation test was now positive at 1:20 dilution. A low serum calcium and an elevated serum phosphate level had been found one month after his initial hospital visit. It was not until these findings were confirmed, six months later, that a clinical diagnosis of hypoparathyroidism was entertained.

TABLE 4.—*Erythrocyte Values During Initial Observation of Case 1**

Sample	Time, Hr.	H_2O	Sodium (mEq./L. of RBC Water)	Potassium (mEq./L. of RBC Water)
1	Adm.	74.9	7.5	137.9
2	41	72.3	0	149.0
3	113	70.5	10.4	136.7
4	161	69.5	23.4	157.7

* Erythrocyte cation was assumed to have been completely dissolved in the cellular water and was calculated on the basis of the following formula: $K_{tw} = K_b - (1 - ht)\ Kp/ht/Kw$, where K_{tw} represents concentration in mEq./L. of erythrocyte water; K_b, concentration in whole blood; ht, hematocrit expressed as a fraction of 1.0; Kp, concentration in plasma, and Kw, water content per liter of packed red cells.

He was admitted in manifest tetany with an upper respiratory infection on June 4, 1955, after he had been requested to return for treatment of his hypoparathyroidism. Polyuria had persisted in varying degree since the previous admission. The skin was less pigmented than previously. Although the beefy-red coloring of the tongue had disappeared, it remained smooth. He responded promptly to treatment with intravenously administered hydrocortisone, calcium, and saline. An

Ellsworth-Howard test was deferred because of a pseudopodial skin response to diluted parathyroid hormone (Parathormone) intradermally. Treatment with vitamin D by mouth, 400,000 units daily, was begun on June 10, 1955. Although orally administered hydrocortisone was increased to 30 mg. daily, appetite and serum sodium and chloride concentrations were decreasing, and desoxycorticosterone acetate (Doca), 4 mg. intramuscularly, and sodium chloride orally were also given. After June 27, 1955, when hormone therapy was changed to cortisone by mouth, 70 mg. daily, there was immediate clinical and subjective improvement. Cultures of the tongue at this time revealed a heavy growth of Candida (Monilia). The hypochromic microcytic anemia was attributed to diagnostic bleeding and responded to oral iron therapy. He was discharged on July 1, 1955, taking daily cortisone by mouth, 50 mg.; sodium chloride, 15 gm.; vitamin D, 100,000 units, and calcium gluconate, 6 gm.

During the succeeding three months tetany recurred once when daily vitamin D was not given regularly. When taking 300,000 units of vitamin D daily he had clinical and chemical improvement. Because of frequent bouts of diarrhea, he was admitted for the third time on Sept. 28, 1955. The physical examination was essentially unchanged. On sigmoidoscopy, the mucosa of the bowel was mildly erythematous but without ulceration or exudate. Candida organisms were cultured from the large bowel wall. Treatment with nystatin (Mycostatin) by mouth, 1,000,000 units daily, was begun. His diarrhea partially subsided on this therapy. After discharge he did well except for two or three loose stools daily. There was little change in the buccal lesions. There may have been less pigmentation. After a seven-hour episode of vomiting and diarrhea, he died at home on Nov. 28, 1955. Postmortem examination was not performed.

CASE 2.—A 6 11/12 year old white boy was seen as an outpatient on Oct. 6, 1955, with the chief complaint of vomiting. Family history was noncontributory. Since the age of 2 or 3 years he had frequent episodes of vomiting and had gained weight poorly. A history of salt-craving since early childhood and of polydipsia and polyuria for an indefinite period was obtained. In June, 1955, he had been hospitalized elsewhere for rubeola. Vomiting subsequently increased in frequency, occurring several times daily during the first week in October, 1955.

On physical examination the pulse rate was 80; blood pressure, 90/40; respiration rate, 20; height, 42 in., and weight, 34 lb. He was a thin well-developed blond fair-skinned delicate boy in no distress. Except for minimal pigmentation about some old scars, the umbilicus, and the scrotum, physical examination was within normal limits. Laboratory determinations are summarized in Table 5. Tuberculin and histoplasmin skin tests were negative. For socioeconomic reasons he was hospitalized elsewhere on Oct. 15, 1955. On Oct. 19, 1955, daily maintenance therapy consisting of intramuscular injections of desoxycorticosterone, 2 mg., and orally administered sodium chloride, 2 gm., was begun and he was discharged home. He gained 5 lb. in one month. On Feb. 3, 1956, hormone therapy was changed to cortisone by mouth, 25 mg. daily. During the next month there was a slight increase in pigmetation, polydipsia, and polyuria, at which time therapy with desoxycorticosterone, 1 mg. intramuscularly every other day, was begun. Since March, 1956, he has been under care at Mt. Sinai Hospital, Chicago.† In February, 1957, he was maintaining good health on replacement therapy.

TABLE 5.—*Laboratory Data in Case 2*

	10/6/55	10/14/55	11/18/55	3/2/56
Na, mEq./L.	108.7	111	137.5	136.2
NPN, mg./100 cc.	47	45	20	24
Cl, mEq./L.	76.6	85.4	103.8	101.4
K, mEq./L.		7.1	4.1	5.2
CO_2, mEq./L.	17.6	18.4	23.4	
Ca, mg./100 cc.			9.8	
P, mg./100 cc.			4.8	
Sugar, mg./100 cc.	56	98	72	
Hgb., gm./100 cc.	13.8	11.0	12.3	13.5
Total eos./cu. mm.		33	678	28
17-Ketosteroids, mg./24 hr.		0.7		
Wt., lb.	34		39 3/4	40 1/2

CASE 3.—A 6 2/12-year-old white boy was first admitted on Oct. 25, 1955, with the chief complaint of nausea.‡ The family history was noncontributory. Two months previously he had been hospitalized elsewhere for pharyngitis, anorexia, nausea, vomiting, easy fatigability, and unsatisfactory weight gain. The above symptoms and abdominal pain recurred two weeks prior to his admission here and necessitated hospitalization and parenteral fluid therapy elsewhere. He had tanned well the previous summer, and his color was somewhat darker than usual. Although he had enjoyed liberally salted food, there had been no history of salt craving. A history of moderate polydipsia and polyuria was obtained. On physical examination the temperature was 99 F; pulse rate, 88; respiration rate, 20; blood pressure, 82/60, and weight, 43 lb. He was a thin sallow chronically-ill white boy. A slight generalized brown pigmentation and several small hyperpigmented areas on the abdominal wall and on one thigh were seen. Physical examination was otherwise within normal limits. Laboratory determinations are summarized

† Dr. Hugo Rony provided detailed information concerning his subsequent course.

‡ Dr. Randolph Batson gave permission for including this case.

TABLE 6.—*Laboratory Data in Case 3*

	10/25/55	11/2/55	11/11/55	2/14/56	7/4/56	10/29/56
NPN, mg./100 cc.	22	27				26
Na, mEq./L.	136.2	102.5	131.2	128.7	125.0	143.7
Cl, mEq./L.	94.8	73.2	87.3	94.2	87.4	98.4
K, mEq./L.	4.5	5.6	3.9	4.4	5.9	4.7
CO_2, mEq./L.	21.7	19.2		26.3	17.2	22.1
TSP, gm./100 cc.	5.3			6.6	7.0	6.7
Albumin, gm./100 cc.	3.2			4.6	4.7	4.5
Ca, mg./100 cc.	10.4			10.0	10.9	10.6
P, mg./100 cc.	2.8		3.6	4.6	5.0	5.2
Sugar, mg./100 cc.	71		78			
Hgb., gm./100 cc.	11.7			13	14	12.3
Total eos./cu. mm.	176			88	102	
17-Ketosteroids, mg./24 hr.			1.7		0.6	2.2
Wt., lb.	43	40	49½	59	59½	

in Table 6. The histoplasmin skin test was positive to 1.0 mg. The tuberculin test was negative. During the first seven days of hospitalization a gastrointestinal series and intravenous pyelograms were performed. The patient became dehydrated and began to vomit during the second of these examinations. The diagnosis of Addison's disease was not made until Nov. 2, 1955, the eighth hospital day, although it had been suspected on admission. Treatment with cortisone, 50 mg. orally, and intravenous dextrose in saline was instituted. He gradually improved on cortisone by mouth, 100 mg. daily, with free access to table salt. He gained 9 lb. and was discharged on Nov. 12, 1955, on daily cortisone, 37.5 mg. orally, and sodium chloride, 1.8 gm. He suffered varicella without complications subsequent to discharge. Because of an appearance like that found in Cushing's disease and a blood pressure of 118/76, he was readmitted on Feb. 14, 1956. At that time the cortisone was decreased to 25 mg. daily. He has subsequently done well with minor alterations in cortisone and sodium chloride intake. At present (September, 1957) his therapy consists of cortisone, 25 mg., and fludrocortisone, 50μg. daily by mouth.

Comment

The association of moniliasis, hypoparathyroidism, and adrenal insufficiency, beginning in childhood and frequently with a familial incidence, has recently emerged as a well-defined syndrome.[9,13] The inclusion of cases reported by previous authors as having only two of the three diseases in this syndrome seems appropriate. Although hypoparathyroidism was recognized before adrenal failure in six of the eight cases reviewed by Whitaker et al., adrenal crises were the presenting endocrinopathy in two of her cases as well as in the present one. It is possible that hypoparathyroidism may yet develop in either of the other two cases in the present report. The rising serum phosphate concentration in Case 3 is being watched with interest, although there has been no other change even suggestive of hypoparathyroidism.

The positive complement-fixation test for histoplasmosis in Case 1 is difficult to interpret, since it was not followed by conversion of the skin test. Unfortunately, this boy died at home, more than 100 miles from the hospital, and news of his death was slow in reaching us. The lack of pathologic findings makes elucidation of this point impossible. The presence of a positive skin test for histoplasmin is a common occurrence in boys of this age in our clinic and can not be interpreted as evidence of active disease in Case 3.

In Case 3 the history suggested the possibility of adrenal failure. Since there was no biochemical evidence to support this diagnosis at the time he was admitted, further studies to determine the cause of his vomiting were carried out. The ensuing iatrogenic dehydration precipitated a mild adrenal crisis, and appropriate therapy was begun.

The erythrocyte cation observations made in Case 1 are reported because no similar observations in children have been found. All the erythrocyte sodium, potassium, and water determinations (Table 4) are within the range seen in normal adults. Compared with the first sample, cell sodium decreased to imperceptible levels at 41 hours. Increases from 41 to 113 and from 113 to 161 hours were observed. An increase in cell potassium

from 0 to 41 and from 41 to 113 hours was also found.

Soft-tissue analyses of various animal species dying in acute adrenal insufficiency have demonstrated that cell water and potassium are increased, with either no change or a decrease in cell sodium.[14-17] Adrenocortical hormone therapy in acute adrenal insufficiency in dogs has been considered to render intracellular water and electrolyte available to the extracellular space.[18] In hypertensive patients subjected to subtotal adrenalectomy, water and potassium have been noted to enter the extracellular compartment under the influence of cortisone.[19] In this patient, as a result of parenteral treatment with steroids, there was a retention of fluid, sodium, and chloride in the first 15 hours. Although precise measurements of intake and output are available only during the first 15 hours, sodium, chloride, and fluid were presumably further retained, since at 41 hours, after adequate oral intake had been reestablished, plasma sodium and chloride increased and the hematocrit value decreased from 37% to 28%. At this time (41 hours) erythrocyte sodium and water had decreased while potassium had increased.

The decrease in erythocyte sodium following cortisone administration is in accord with the observations of Wilson and Miller[20] that the total exchangeable sodium as measured with Na^{24} decreased after cortisone therapy in patients with Addison's disease having abnormal electrocardiograms while the extracellular sodium concentration and volume were increasing.

The significance of the increase in cell sodium and the slight absolute decrease in cell potassium at 161 hours is not clear. In the preceding 24 hours, cortisone maintenance had been decreased from 50 to 25 mg. daily. These changes may have been associated with relative adrenal insufficiency incidental to the decrease in cortisone administration.

Neither opportunity nor facilities for measuring the lack of response of these three patients to corticotropin stimulation were available. All three patients were in adrenal crisis when first seen and responded rapidly to parenteral therapy with cortisone or its derivatives, sodium chloride, glucose, and water. In none of them was pituitary failure suspected on clinical grounds. In the first patient our attempts to educate his family concerning the need for medical care at the onset of any illness proved to be inadequate. The availability of parenteral replacement therapy in the home might have saved this boy's life. The rapidity of onset of adrenal crisis in this age group makes early recognition of this disease a challenge.

Summary

Three cases of Addison's disease in 6-year-old boys are reported. One patient also had hypoparathyroidism and moniliasis and died. Since 5 of 12 reported patients with Addison's disease aged 10 years or younger had hypoparathyroidism and/or moniliasis or a sibling with this syndrome, it should be looked for in all cases. Similarly, cases of hypoparathyroidism should be watched for the development of adrenal insufficiency.

School of Medicine, Vanderbilt University (Dr. Woodruff).

REFERENCES

1. Jaudon, J. C.: Addison's Disease in Children, J. Pediat. 28:737-755, 1946.

2. Burdick, W. F.; Warthen, R. O.; Cassidy, J. E., and Welsh, W. W.: Addison's Disease in a 5½-Year-Old Boy, Am. J. Dis. Child. 80:975-981, 1950.

3. White, F. P., and Sutton, L. E.: Addison's Disease in a Negro Child, J. Pediat. 37:778-782, 1950.

4. Russell, A., and Potter, C. T.: Addison's Disease in Childhood, Proc. Roy. Soc. Med. 44:957-960, 1951.

5. Mautner, H.: Addisonian Crisis in a Boy of 4 Years of Age, Bibl. paediat. Basel., No. 58, pp. 354-360, 1954.

6. Bickel, H., and Stamm, O.: Über einem Fall von Morbus Addison im Kindesalter infolge Nebennierencirrhose, Helvet. pædiat. acta 3:53-63, 1948.

7. Bie, J.: Morbus Addisonii hos børn: Forekomst hos 2 søskende, Nord. med. 55:193-198, 1956.

8. Talbot, N. B.; Butler, A. M., and MacLachlan, E. A.: The Effect of Testosterone and Allied Compounds on the Mineral, Nitrogen, and Carbohydrate Metabolism of a Girl with Addison's Disease, J. Clin. Invest. 22:583-593, 1943.

9. Craig, J. M.; Schiff, L. H., and Boone, J. E.: Chronic Moniliasis Associated with Addison's Disease, A. M. A. Am. J. Dis. Child. 89:669-684, 1955.

10. Cabot Case 40361, New England J. Med. 251:442-448, 1954.

11. DiGeorge, A. M., and Paschkis, K.: The Syndrome of Addison's Disease, Hypoparathyroidism, and Superficial Moniliasis, A. M. A. Am. J. Dis. Child. 94:476-478, 1957.

12. Williams, A., and Robinson, M. J.: Addison's Disease in Infancy, Arch. Dis. Childhood 31:265-269, 1956.

13. Whitaker, J.; Landing, B. H.; Esselborn, V. M., and Williams, R. R.: The Syndrome of Familial Juvenile Hypoadrenolcorticism, Hypoparathyroidism and Superficial Moniliasis, J. Clin. Endocrinol. 16:1374-1387, 1956.

14. Harrison, H. E., and Darrow, D. C.: The Distribution of Body Water and Electrolytes in Adrenal Insufficiency, J. Clin. Invest. 17:77-86, 1938.

15. Darrow, D. C.; Harrison, H. E., and Taffel, M.: Tissue Electrolytes in Adrenal Insufficiency, J. Biol. Chem. 130:487-502, 1939.

16. Muntwyler, E.; Mellors, R. C.; Mautz, F. R., and Mangun, G. H.: Electrolyte and Water Equilibria in the Dog: II. Electrolyte and Water Exchange Between Skeletal Muscle and Blood in Adrenal Insufficiency, J. Biol. Chem. 134:367-387, 1940.

17. Buell, M. V., and Turner, E.: Cation Distribution in the Muscles of Adrenalectomized Rats, Am. J. Physiol. 134:225-239, 1941.

18. Swingle, W. W.; Parkins, W. M.; Taylor, A. R., and Hays, H. W.: A Study of Water Intoxication in the Intact and Adrenalectomized Dog and the Influence of Adrenal Cortical Hormone upon Fluid and Electrolyte Distribution, Am. J. Physiol. 119:557-566, 1937.

19. Hills, A. G.; Chalmers, T. M.; Webster, G. D., Jr., and Rosenthal, O. H.: Adrenal Cortical Regulation of the Distribution of Water and Electrolytes in the Human Body, J. Clin. Invest. 32:1236-1247, 1953.

20. Wilson, G. M., and Miller, H. E.: Exchangeable Sodium in Addison's Disease in Relation to the Electrocardiogram and the Action of Cortisone, Clin. Sc. 12:113-129, 1953.

Speech- and Language-Handicapped Children

ISAAC W. KARLIN, M.D., Brooklyn

In general usage the terms speech and language are used interchangeably. Semantically one has to differentiate between speech and language. Language in its widest sense signifies the elaboration of thoughts and ideas. Language and thought are intimately related and mutually influence each other. Spoken words are arbitrary audible symbols, and propositional, that is, meaningful, speech may be regarded as verbal means of communication, a tool and a manifestation of language.

From a phylogenetic point of view, speech is the newest of man's skills. For its normal development one must have a normally functioning brain, adequate hearing, normal peripheral anatomical structures used in speech, and also a stimulating environment.

These peripheral structures are not special organs set aside solely for speech. Speech has arrogated to itself structures such as the mouth, lungs, and larynx that biologically perform more vital and quite different functions. The central nervous system acts as an integrator of these organs that are otherwise dissociated in function, and it is only in the brain that certain areas have been developed whose function is predominantly concerned with speech.

There are still differences of opinion as to the specificity of function of certain areas of the brain. Some hold that there is pinpoint specificity and that the function of speech is localized in definitely circumscribed areas—so-called centers; others doubt this specialization and postulate that speech is the function of the entire cortex.[1]

The term brain center has lately been more clearly defined by Nielsen.[2] He points out that center does not mean a delimited cortical zone with independent functional capacity but that it is rather an anatomically delimited zone which is essential to a certain function. In this presentation the term center will be used only in the latter sense.

The normal activity of the central nervous system depends upon the interaction of sensory and motor systems. The sensory, or receptive, component of speech consists of comprehending spoken or written language, i. e., spoken words or written symbols. The motor or expressive component of speech consists in the ability to express words or written symbols. In the development of speech, associations are formed between verbal sounds or words and meaning. This is the child's first goal in speech development. The child must first receive the spoken words for a certain period of time in order for the symbols to acquire their characteristic meaning. After hearing and understanding spoken words, he begins to talk. The sequence of events is as follows: receptive speech—inner speech—expressive speech.

The auditory word area for the comprehension of spoken language is in the superior temporal gyrus, Areas 41 and 42—Wernicke's area. There is evidence that the adjoining portion of Area 22 subserves the same function. Area 37 is the language formulation area, where engrams are laid down for the proper arrangement of words into sentences. Area 17 is the primary visual center. Areas 18 and 19 are the secondary visual centers concerned with recognition of objects but not with symbols.

Submitted for publication July 10, 1957; accepted Sept. 6.

From the Speech Clinic, Pediatric Department, Jewish Hospital of Brooklyn.

Presented at the 10th Postgraduate Seminar in Psychiatry and Neurology, Yale University School of Medicine, New Haven, Conn.

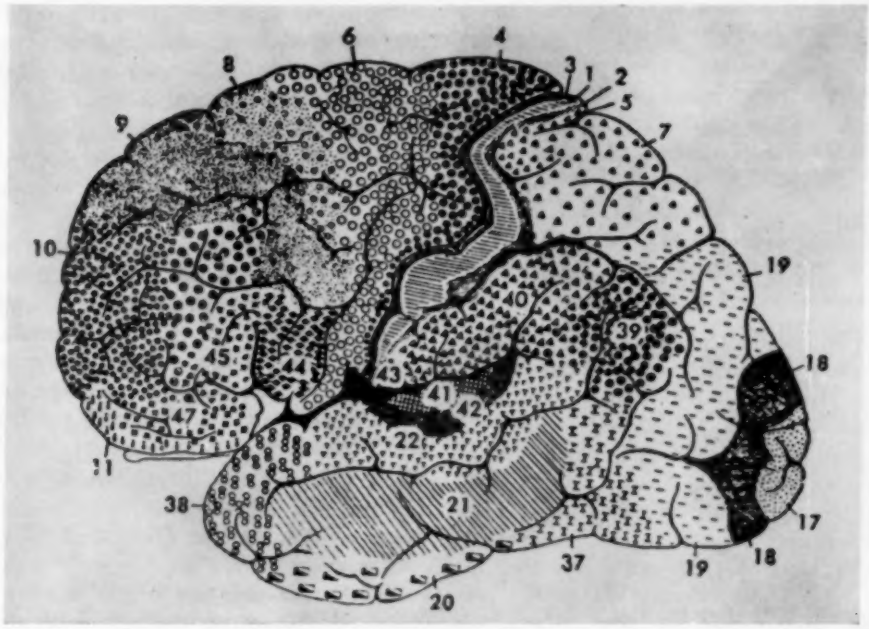


Fig. 1.—Cytoarchitectonic fields of the human cerebral cortex. (From Brodman [1909].)

Area 39 is the visual word area. Area 44, Broca's convolution, is the motor or expressive area and is located at the posterior end of the inferior frontal convolution. The writing area is part of the cheirokinesthetic area and is situated above Broca's area (Fig. 1).

Another distinctive feature in speech function is the dominance of one cerebral hemisphere over the other, and this is related to handedness, since in right-handed persons the left cerebral hemisphere is the dominant or major hemisphere. The evidence for this is that right hemiplegia is usually accompanied by a language disorder, whereas this is not true for left hemiplegia. The infant uses both hands randomly. As the child grows older, there is a simultaneous development of higher mental functions, cerebral dominance, handedness, and language function. It would appear that these are all interrelated. Orton [3] and Gesell [4] have emphasized the importance of cerebral dominance in relation to laterality and language functioning. In a previous report by Karlin and Strazzula [5] it was shown that there is a relationship between cortical development, language development, and the establishment of handedness.

The findings were that the group with the higher I. Q. had a greater percentage of established handedness. These results were statistically significant. It was also noted that the children with higher I. Q.'s had better language ability. This study indicates that a positive correlation exists between the degree of brain development, the development of language, and handedness (Table).

There are certain factors that normally influence the development of speech in the child. 1. Sex. Girls begin to talk earlier than boys; the average for girls is 17 to 18 months; for boys, 19 to 20 months. As they grow older girls continue to excel boys in linguistic development. 2. General intelligence. Mentally retarded children will begin to talk later than the children of normal intelligence. The greater the retardation the

Per Cent of Children in Whom Handedness is Established in Relation to Intelligence Quotient

I. Q. Range	C. A.*	M. A.†	Handedness Established, %
15–25	3 yr. 9 mo. to 14 yr. 0 mo.	0 yr. 6 mo. to 3 yr. 9 mo.	56
26–50	3 yr. 0 mo. to 13 yr. 7 mo.	1 yr. 3 mo. to 6 yr. 0 mo.	65
51–70	3 yr. 9 mo. to 14 yr. 1 mo.	1 yr. 8 mo. to 7 yr. 11 mo.	92

* Chronological age.
† Mental age.

later will be the onset of speech. 3. Socioeconomic and environmental factors. Children from cultured homes are more advanced linguistically. These children are exposed to a better language influence and stronger motivation. The concept, however, that lack of stimulation will delay language development has been overemphasized. 4. Twins, since they habitually play together, are least under pressure to acquire language and usually are slow in acquiring speech. Only children, whose companions are mainly adults, acquire speech most rapidly. Non-twins with siblings, and therefore having as companions both adults and children, acquire speech at a time intermediate between that of twins and that of only children.

Speech and language disorders may be classified as follows:

1. Delayed speech—retardation in acquisition and use of words
2. Articulatory disorders—the distortion, omission, and substitution of consonant sounds
3. Voice disorders—the absence of voice or abnormal production of the qualities (intensity, pitch, or melody) of voice
4. Cluttering—rapid speech, associated with slurring and distortion of sounds
5. Stuttering—disorganization of the rhythmic flow of speech
6. Aphasias—disorders of linguistic symbolization

It is evident that disorders of speech will result from such grossly discernible defects as cleft palate, cerebral palsy, nasal obstruction, laryngeal anomalies, and various muscle paralyses. The challenging problems in the language field are those which to the usual good clinical methods of evaluation show a paucity of somatic deficiencies.

These problems may be roughly divided into two groups: A. Children 2 to 5 years of age who either do not talk at all or have very limited or distorted speech. B. Children who stutter.

A. With children in the first group the differential diagnosis involves the following considerations.

1. Deafness. Does the child hear? This has to be answered when a child 2 to 5 years old does not talk or has very limited speech. A great deal of valuable information about the child's hearing ability may be obtained from a detailed developmental history and from clinical observation of the child's total behavioral pattern.

The newborn infant with normal hearing responds to loud noises with a startle reaction—a sudden start or twitch of the face or entire body. Soon afterward he may respond to sound in the form of a reflex—palpebral winking or pupillary contraction. Between 3 and 6 months of age the infant begins to relate hearing and vision. He localizes sounds by turning his eyes or head to the source, as on hearing mother's footsteps or closing of the door.

An important phase in the development of speech and hearing, which is frequently overlooked, is the "babbling period." Babbling, which is a pleasurable use of vocalization, appears at about 3 or 4 months of age. At this stage babbling is purely a reflexive phenomenon, a response to some internal stimulation. During the second half of the first year the infant babbles more and more, and there is a great deal of repetition of the same sound or combination of sounds. This latter form of babbling, which is often called the lalling period, is a conditioned response. The infant hears the sound of his voice, and this auditory experience sets off a motor response. Hearing and sound production have become associated. It is interesting to note that even a deaf child begins to babble after a fashion just like the normal-hearing child. The deaf infant as he grows older grad-

ually babbles less and less and may even stop babbling completely.

The older child with a hearing defect relies heavily on vision. He watches his environment and watches his mother's face and lips when she talks to him. He may use a great many gestures to indicate his needs. His voice is harsh and monotonous. He may smile and laugh less than the normal-hearing child. He tends to be more introverted and emotionally less well balanced. Valuable simple hearing tests can be made in the office with use of sound toys such as a squeaking doll, a horn, a rattle, or a whistle. A child is much more likely to respond to mixed sounds made by sound toys than to pure sounds made by the audiometer. One may have to enlist the mother's assistance, and one has to depend a great deal upon the cessation of activity technique—the child momentarily ceases his play when the sound is produced. With the older child speech and voice may be used as a source of sound.

Hearing tests which are satisfactory for adults cannot be used with young children. Pure-tone audiometry is a subjective test, and responses cannot be achieved until the mental and perceptual level is at least that of the average 5- or 6-year-old child.[6,7] The objective tests, such as psychogalvanic audiometry, the peep-show technique, and electroencephalography, are valuable but rather complicated tests. They need the services of highly trained personnel and even in their hands these tests are not infallible. Hearing estimation in a young child should be made on the basis of a detailed history, clinical observation and evaluation, and then laboratory investigation.

2. Congenital word deafness. A much more difficult diagnostic problem presents itself when a child apparently is able to hear sounds but does not respond to the spoken word.

This problem may be illustrated by a child of 3 or 4 years old who has either very limited speech or no speech at all. The developmental history is normal. Physical examination is negative. Mentally the child appears to be normal. Parents are certain that the child hears sounds. This is substantiated by the clinical observation that the child responds to sound toys. Psychogalvanic audiometry indicates that the child can hear. It is evident, however, that the child is "deaf" to speech.

It is assumed that this disorder is due to a defect or delay in development in the cortical temporal areas where it is believed that the analysis, recognition, and comprehension of spoken language takes place. For this congenital word deafness I have suggested the term congential verbal auditory agnosia.[8] This is descriptive in the sense that it indicates the defect to be on a lower order than aphasia and it localizes the defect to the cortical hearing and speech areas. Agnosia of language, however, belongs to aphasia, and the term aphasia is a good generic term, since it denotes a cerebral form of language dysfunction.

3. Mental retardation. In this condition there is a general delay in physical and mental growth. In the development of speech there is a greater delay than in the onset of predominantly motor activities such as sitting and walking. There is also, in comparison with the normal, a greater lag between the onset of words and the onset of simple sentences. It is well to remember that mutism or complete failure of speech to develop can be ascribed to mental retardation only when the amentia is on the level of the low-grade idiot.[5]

4. Schizophrenia. The early developmental history may be entirely normal. As the child grows older he may not pay attention to his surroundings and his behavior is odd and bizzare. When schizophrenia occurs in the first few years of life, before language is well established, there may be complete mutism. This may be later overcome with speech which is markedly distorted. When speech has already been established, it may gradually deteriorate or regress by use of simpler forms. Speech may be explosive, aggres-

sive, or obscene. The patient does not use speech as a means of communication or interpersonal relationship. Speech is used as a repetetive expression of anxiety, the child never waiting for an answer. In some cases there may be an early precocious language development, but the speech is fragmentary, dissociated, and bizarre, as if the child were experimenting with many alternate thoughts and ideas.[9]

5. Autism. Autism may be regarded as a form of schizophrenia. As far as speech is concerned, the child may remain mute, but the majority acquire the ability to speak. Speech, however, even when present, does not serve to convey meaning to others. Naming presents no difficulty; the child may remember long and unusual names. Delayed echolalia is present; i. e., he may repeat at a later date a word or a sentence he heard a day or two before.[10]

6. Brain-injured child. This terminology has become increasingly popular since the work of Strauss and Lehtinen.[11] Children who are brain-damaged during prenatal growth, at birth, or soon after birth, if they are not grossly mentally retarded, will often exhibit language difficulties as their outstanding presenting problems. These children have not achieved distinct cortical functional organization. Neurological examination may reveal a questionable Babinski sign, nystagmus, or paralysis of some cranial nerves. Very often physical and neurological examinations as well as the electroencephalogram will be entirely normal. The psychological tests may reveal the child to be of borderline intelligence. This is usually qualified as being minimal owing to the child's verbal and language limitations. The psychologist will frequently report signs of "organicity," such as a poor visual-motor coordination, distortion of human figure drawing, or poor motor coordination as in dressing or buttoning. The child may have no speech at all. Usually he does have some vocabulary and he may surprise one from time to time with the actual number of words he knows; his sentence structure, however, is very limited and agrammatism is common. Hearing is good, but he shows marked irritability and distractibility. At times he may respond immediately to a simple question; at other times one has to repeat the question again and again before some response is made.

B. Stuttering. The largest group of speech-handicapped children belongs to this category. The problem of stuttering is as old as the human race; it has been recorded in the Bible. A stutterer may continue to stutter, to a greater or less degree, throughout his entire life. Since speech is essentially a social activity, the symptomatology will naturally vary, depending on at what age period one sees the stutterer—the preschool child, the school child, the adolescent, or the adult.

The theories about the pathogenesis of stuttering can be divided into (1) functional and (2) organic. The definition of a theory as given by the "Encyclopaedia Brittanica" is, "A tentative explanation of phenomena framed to agree with observed facts and designed as a rational explanation of them." Now, what are the basic facts about stuttering? The onset of stuttering is between 3 and 4 years of age. It occurs in about 1% or 2% of the school population. It is commoner in males than females, the proportion is 4 or 5:1. It occurs at all levels of the scale of intelligence. It has a familial predisposition. There are fewer adult stutterers than child stutterers, because some stutterers as they grow older, even with no therapy, stop stuttering and acquire fluent speech.

The functional theories reflect the attitudes of the age group of the stutterers one sees, as well as the prevalent concepts of today in psychiatry and psychology. These theories postulate that stuttering is no different from the occasional hesitations of the nonstuttering child or adult. Second, they say that stuttering develops as a result of the fears, threats, and apprehensions of anxious parents, which tend to fix the child's attention on the speaking situation. In brief,

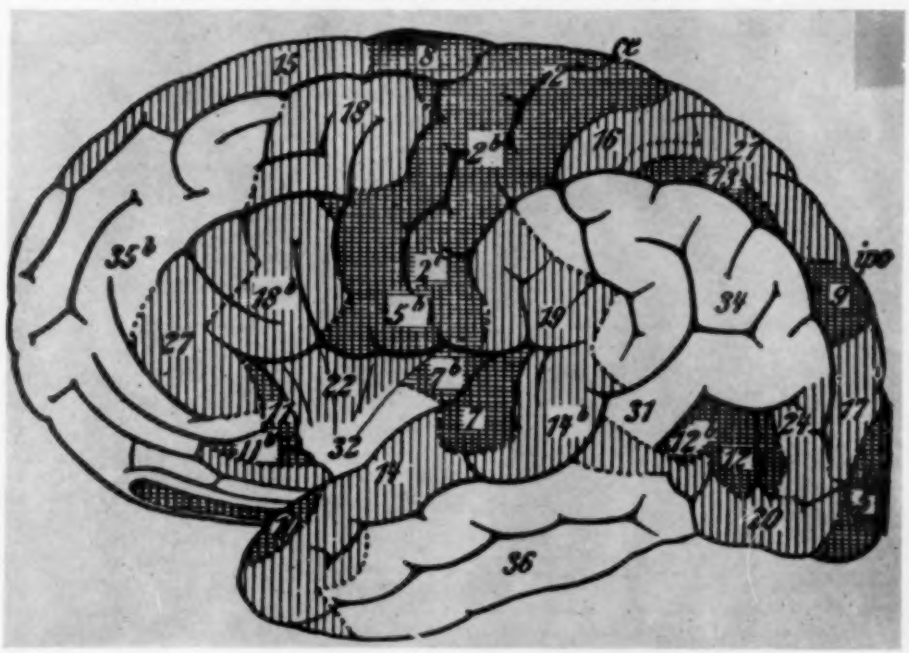
according to these theories stuttering is due to disturbed parental and environmental factors.

A news magazine published for parents of young children, *2- to 5-World News*,[12] summarizing my recent publication on stuttering,[13] comments, "It's *sometimes hard* for the parents of a stuttering child to look their family physician in the eye. So many speech authorities have named undue parental anxiety about a youngster's normal speech repetitions as a focal factor in stuttering that a parent hates to admit he's even *noticed* that his child stutters, let alone ask for help!"

Another concept of stuttering is that, with recognition that psychologic and environmental factors play an important role, it basically is an organic disorder. Stuttering, according to this theory, is basically due to a delay or to a slower progress of myelinization of the cortical association areas concerned with speech. Myelinization is regarded as correlated with function. It has been established that (1) myelinization occurs earlier in girls than in boys; (2) myelinization does not proceed at a uniform rate (there are periods of acceleration and periods of decreased velocity); (3) myelinization proceeds in the following order: the sensory, the motor, and the association fibers. Figure 2 illustrates the order of myelinization of the various areas of the brain. As can be seen, cortical areas concerned with speech myelinate late.

The theory that stuttering is basically due to a retarded or delayed process of myelinization helps to explain the basic facts about stuttering. Stuttering occurs oftener in boys because myelinization begins earlier in girls. By the time the girl is 3 or 4 years old the myelinization of her speech areas in the brain is apt to be more advanced than that of the boy. Since myelinization may not be complete until 20 years of age, this may be the reason why some stutterers outgrow

Fig. 2.—Lateral view of the human cerebral hemisphere, showing the cortical areas as outlined by Flechsig on the basis of differences in the time of myelination of their nerve fibers. The primary areas (first to become well myelinated) are cross hatched; the intermediate are indicated by vertical lines; the late areas are unshaded. (Lewandowsky.)



their difficulty as they grow older and more mature.

The physician, or more likely the pediatrician, is usually the first one to see the child who stutters. The time-honored advice given is, "Leave him alone; he will outgrow it." The speech therapist today tells the mother, "This is not stuttering; it is only nonfluency," a euphemism which only disguises the seriousness of the problem. The best time for treatment and the best results obtained in the treatment of stuttering are in its inception. Early treatment was advocated years ago,[14,15] and it is still most desirable today.

41 Eastern Pkwy (38).

REFERENCES

1. Karlin, I. W.: Aphasias in Children, A. M. A. Am. J. Dis. Child. 87:752, 1954.

2. Nielsen, J. M.: Agnosias, Apraxias, Speech, and Aphasias, in Clinical Neurology, edited by A. B. Baker, New York, Paul B. Hoeber, Inc. (medical book department of Harper & Brothers), 1955.

3. Orton, S. T.: Reading, Writing and Speech Problems in Children, New York, W. W. Norton & Company, Inc., 1937.

4. Gesell, A., and Amatruda, C. S.: Developmental Diagnosis, New York, Paul B. Hoeber, Inc. (medical book department of Harper & Brothers), 1948.

5. Karlin, I. W., and Strazzula, M.: Speech and Language Problems of Mentally Deficient Children, J. Speech Disorders 17:286, 1952.

6. Mc Laurin, J. W.: The Inarticulate Child, Laryngoscope 64:455, 1954.

7. Myklebust, H. R.: Auditory Disorders in Children, New York, Grune & Stratton, Inc., 1954.

8. Karlin, I. W.: Congenital Verbal-Auditory Agnosia (Word Deafness), Pediatrics 7:60, 1951.

9. Bender, L.: A Dynamic Psychopathology of Childhood, Springfield, Ill., Charles C Thomas, Publisher, 1954.

10. Kanner, L.: Child Psychiatry, Springfield, Ill., Charles C Thomas, Publisher, 1950.

11. Strauss, A. A., and Lehtinen, L. E.: Psychopathology and Education of the Brain-Injured Child, New York, Grune & Stratton, Inc., 1947.

12. 2- to 5-World News 5:4 (Feb.) 1957.

13. Karlin, I. W.: Stuttering: Evaluation and Treatment, New York J. Med. 56:3719, 1956.

14. Karlin, I. W., and Kennedy, L.: Stuttering: Problem and Suggested Treatment, Am. J. Dis. Child. 55:383, 1938.

15. Karlin, I. W.: Stuttering—The Problem Today, J. A. M. A. 143:732, 1950.

Renal Vein Thrombosis

1. Age Incidence in Infancy and Childhood; 2. Sex Incidence; 3. Incidence of Unilateral and Bilateral Involvement

HERBERT J. KAUFMANN, M.D., Boston

The diagnosis of renal vein thrombosis is rarely entertained in infants beyond the first months of life, owing largely to statements that the majority of cases occur in the neonatal period. This paper is based on a clinically suspected and successfully operated-on case of renal vein thrombosis in a one-year-old girl. This is the second case reported with survival in the second year of life. In 1953, Mills and Owen [1] reported their case, in an 18-month-old girl, with the following comment: "With the exception of Kobernick et al., we have not found any record of the condition occurring in the second year of life." It is our purpose to review the available literature with reference to the age incidence of renal vein thrombosis. During the course of the search of the literature, we also became interested in the incidence of unilateral and bilateral involvement in published series, and the present review includes this aspect of the problem.

Report of a Case

A one-year-old white girl was admitted on Dec. 21, 1956, with the chief complaint of fever, irritability, and an episode of vomiting of 12 hours' duration. The patient had previously been hospitalized because of aseptic meningitis and had been discharged from the hospital a week prior to this admission.

Physical Examination.—Temperature, 103 F; pulse rate, 160; respirations, 28. Height, 81 cm.; head circumference, 45 cm.; chest, 50 cm.; abdomen, 48 cm. The patient was a well-nourished child with grunting respirations. The skin showed a generalized erythema and a diaper rash. There was injection of the pharynx and left ear drum. The neck was negative. There was slight dullness at the right base, and breath sounds were diminished over this area. No rales were heard. The abdomen was soft. No masses were noted, and there was no enlargement of liver, spleen, or kidneys. Extremities were normal, and neurological examination was negative.

Laboratory Studies.—Urinalysis: yellow, acid, with albumin 3+, ketones 2+, RBC 5-7, WBC 7. Hemoglobin was 5 gm.; WBC, 32,600, with a marked shift to the left. NPN was 23 mg/100 cc.; fasting blood sugar, 120 mg/100 cc.; CO_2, 15.5 mEq. per liter; chloride, 117 mEq. per liter; potassium, 5 mEq. per liter, and sodium, 137 mEq. per liter. Throat culture showed β-hemolytic streptococci. Nasopharyngeal culture showed β-hemolytic streptococci. Blood culture revealed no growth. Urine culture yielded Escherichia coli. Lumbar puncture yielded clear fluid with a total protein of 20 mg/100 cc.; sugar, 80 mg/100 cc., and chlorides, 783 mg/100 cc. Chest x-ray revealed a pneumonitis at the right base.

Course in Hospital.—At the time of admission the clinical impression was acute pharyngitis, otitis media, and possible right lower lobe pneumonitis. Penicillin and streptomycin were started; the temperature gradually declined but did not reach normal, rising again on the sixth hospital day. Lumbar puncture was repeated but was again normal. The urine was yellow and acid, with albumin 2+ and sugar 2+. There were numerous red blood cells per high-power field and occasional white blood cells. The sediment was loaded with bacteria, granular casts, and crystals. The nonprotein nitrogen had risen to 68 mg. The child continued to have high fever and became generally pale and dry. Examination at this time revealed a rather firm tender immovable mass over the right lumbar region. The differential diagnosis included perinephric abscess, periappendiceal abscess, and renal vein thrombosis. A flat plate of the abdomen was interpreted as normal. Intravenous fluids and transfusion were given, and tetracycline (Achromycin) was started. An intravenous pyelogram showed absence of dye in the right kidney. Cystoscopy yielded no urine from the right side; retrograde pyelography showed a normal left ureter and kidney but a block from the midureter upward on the right. These findings appeared to make a diagnosis of renal vein thrombosis most

Received for publication Oct. 1, 1957.

From the Department of Pediatrics, Boston University School of Medicine, and the Pediatric Service of The Boston City Hospital.

likely. Through a right lumbar incision thrombosis of the right renal vein and adrenal vein were found, together with an enlarged hemorrhagic kidney. The right kidney and adrenal were removed. Postoperatively, the patient showed dramatic improvement, becoming afebrile in 24 hours. The nonprotein nitrogen fell to 23 mg., and the urine cleared rapidly. Pallor disappeared, and the child became active again. She was discharged in good condition on the 14th postoperative day.

Final Diagnosis.—Renal vein thrombosis, right; diffuse hemorrhagic infarction of right kidney and right adrenal gland; perirenal hemorrhage, right.

Pathology Report.—Multiple thrombosis of the right renal and intrarenal veins; diffuse hemorrhagic infarction of the right kidney; diffuse recent and organizing perirenal hemorrhage; periadrenal hemorrhage.

Follow-Up.—The infant was seen at 10 days, 1 month, and 6 months after discharge and showed excellent progress, with normal growth and development. A repeat intravenous pyelogram revealed normal function of the left kidney, with good outline of the left ureter and prompt filling of the bladder.

Review of the Literature

There is little information concerning renal vein thrombosis in modern textbooks of pediatrics. We could find no mention of this condition in books by Holt and McIntosh,[2] Paterson and McCreary,[3] Sheldon,[4] Slobody,[5] Fanconi and Wallgren,[6] Glanzmann,[7] Potter,[8] Gross,[9] Caffey,[10] and Lassrich et al.[11] Nelson's textbook [12] discusses renal vein thrombosis in a small paragraph on hemorrhagic infarction of the kidney, focusing entirely on the newborn period. "Brennemann's Practice of Pediatrics" [13] devotes a short paragraph to the problem, again with emphasis solely on its occurrence in the neonatal period. Davison's text [14] merely mentions its existence.

This dearth of information is unfortunate in view of Campbell's statement [15] that the mortality rate can be reduced from 95% to 25% in cases of unilateral renal vein thrombosis by prompt surgical intervention and is surprising in view of the fact that since 1942 there have been 20 articles on the subject in the Anglo-American literature alone. Older German texts, such as Finkelstein's "Diseases of Infancy," published in 1925,[16] and the classic "Handbuch der Kinderheilkunde," edited by Pfaundler and Schlossmann in 1924 [17] refer to this condition at some length.

The best presentation is given in the textbook on pediatric urology by Campbell,[18] who is most qualified to write on renal vein thrombosis, since, in addition to reporting the first nephrectomized cases with survival in the United States, he was able to arrive at a correct preoperative diagnosis for the first time in his second patient.[15] Discussing the problem of age predilection, he states, "Most cases of renal vein thrombosis occur during the early weeks and months of life." He maintains that up to 1951 "only 26 cases in the young have been reported in the literature," and that he knows of "50 unreported cases discovered at autopsy, almost all of which were infants." [18]

The emphasis in the literature on renal vein thrombosis as a problem to be considered in the neonatal period and the present case in a one-year-old infant led to a survey of the age distribution of this condition in childhood.

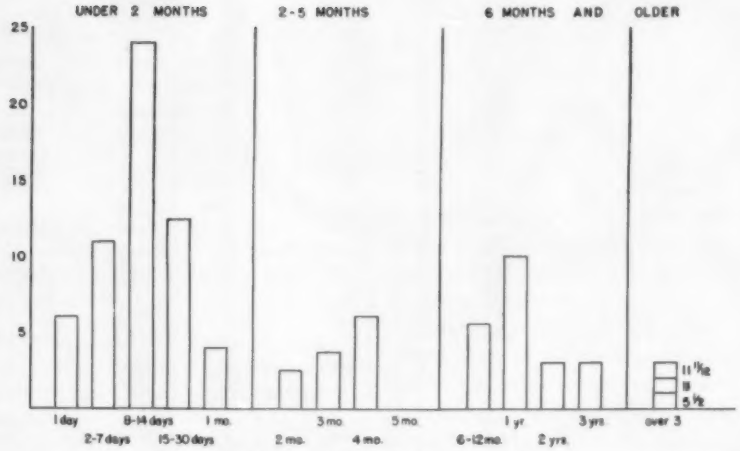
Age Distribution of Renal Vein Thrombosis.—In the most extensive review of the literature to date, Abeshouse, in 1945,[19] collected a total of 228 cases of renal vein thrombosis in all age groups. Of these, 112 occurred in children under 2 years of age, with 90 cases under 2 months of age and 22 cases over 2 months of age. He listed 11 cases from 1 to 5 years of age and 3 cases from 5 to 10 years of age. Since information prior to 1900 is poorly documented and fragmentary, we have included in the present survey only those cases reported since 1900 (Table 1).*

*This list does not include cases of hemorrhagic infarction of one or both kidneys in the absence of renal vein thrombosis (Giampalmo,[20] Marshall and Wapham,[21] Milburn,[22] Oppenheim,[23] Pontieri,[24] and others). Also, cases with thrombosis of the smaller intrarenal venous tributaries are omitted. From the entire series of Morison [25] we include only Cases 12 and 14, and from Zuelzer's material [26] we have listed only the cases of renal vein thrombosis of the main renal vein and those involving the larger intrarenal veins showing similar pathology.

TABLE 1.—*Summary of Cases Reported Since 1900*

Author *	Year	Case	Age	Sex	Side Involved	Origin
Fahr [24]	1903	1	2 mo.	F	Left	Germany
		2	2 yr.	F	Bilateral	
		3	8 mo.	M	Left	
		4	1 ½ yr.	M	Left	
Richardière & Merle [26]	1910	5	15 mo.	M	Left	France
Wirtz [27]	1910	6	14 days	F	Left	Germany
Heller [28]	1923	7	9 days	M	Bilateral	Germany
Petremand [29]	1923	8	8 days	F	Bilateral	Switzerland
		9	2 days	M	Bilateral ?	
Finkelstein [19]	1925	10	7 days	F	Left	Germany
Schröder [30]	1926	11	4 mo.	F	Bilateral	Germany
		12	9 mo.	M	Right	
		13	?	M	Right	
		14	1 mo.	M	Bilateral	
		15	5 ½ yr.	M	Left	
Aschner [31]	1927	16	2 mo.	M	Right	United States
Färber & Bussel [32]	1930	17	2 yr.	F	Bilateral	Germany
Eilers [33]	1930	18	15 days	M	Bilateral	Germany
Nordwall [34]	1932	19	2 wk.	F	Bilateral	Sweden
Grüneberg [35]	1932	20	3 mo.	F	Left	Germany
Hepler [36]	1934	21	2 ½ yr.	F	Bilateral	United States
		22	7 mo.	F	Left	
Behr [37]	1938	23	9 yr.	M	Right	Netherlands
		24	3 yr.	F	Left	
		25	15 mo.	F	Bilateral	
		26	1 yr.	F	Bilateral	
		27	3 wk.	M	Right	
		28	1 ½ yr.	M	Right	
Wegelin [38]	1938	29	3 yr.	F	Bilateral	Switzerland
Hesse [39]	1940	30	1 day	F	Left	Germany
Perry & Taylor [40]	1940	31	11 yr.	M	Left	United States
Ungari [41]	1940	32	9 mo.	F	Bilateral	Italy
Barenberg et al. [42]	1941	33	3 days	?	Right	United States
		34	13 days	?	Right	
Campbell & Matthews [44]	1942	35	13 days	M	Right	United States
		36	29 days	M	Right	
Koopmann [43]	1944	37	1 yr.	F	Bilateral	Germany
Morison [45]	1945	38	12 days	F	Bilateral	England
		39	8 days	M	Bilateral	
Thurston [46]	1947	40	7 days	M	?	United States
Lapointe [47]	1947	41	7 days	?	Right	France
		42	30 days	?	Right	
		43	13 days	?	Bilateral	
Sandblom [48]	1948	44	5 days	F	Left	Sweden
Freund & Bick [49]	1949	45	4 ½ mo.	M	Bilateral	Germany
		46	3 ½ mo.	?	Right	
		47	3 wk.	?	Left	
Fallon [50]	1949	48	16 days	M	Bilateral ?	England
		49	12 days	M	Right	
		50	4 wk.	F	Bilateral	
		51	1 day	F	Bilateral	
Smith & Arey [52]	1950	52	3 mo.	M	Left	United States
McClelland & Hughes [51]	1950	53	8 days	M	Bilateral	United States
		54	11 days	F	Left	
		55	12 days	M	Bilateral	
Ferloni et al. [53]	1951	56	4 mo.	M	Bilateral	United States
Kobernick et al. [54]	1951	57	3 wk.	F	Bilateral	Canada
		58	2 mo.	F	Right	
		59	1 mo.	M	Right	
		60	14 mo.	F	Bilateral	
Parry [55]	1951	61	10 days	M	Left	England
Zuelzer et al. [56]	1951	62	2 wk.	F	Bilateral	United States
		63	4 days	F	Bilateral	
		64	2 days	F	Left	
		65	6 mo.	F	Bilateral	
		66	8 days	F	Bilateral	
		67	9 days	F	Bilateral	
		68	4 ½ mo.	F	Right	
		69	3 yr.	M	Left	
DeCamp et al. [57]	1951	70	2 wk.	?	?	United States
Buchtel [58]	1951	71	9 days	M	Left	United States
Warren et al. [59]	1953	72	9 days	M	Left	United States
		73	1 day	M	Right	
Clark & Pickup [60]	1953	74	10 days	F	Left	England
Clatworthy et al. [10]	1953	75	7 days	M	Left	United States
		76	1 day	?	Bilateral	
Mills & Owen [1]	1953	77	18 mo.	F	Left	England
Puccini [62]	1953	78	3 mo.	F	Left	Italy
Stevens & Tomsykoski [61]	1954	79	19 mo.	F	Bilateral	United States
Children's Hospital, Washington, D. C. [63]	1954	80	4 mo.	M	Bilateral	United States
Ahvenainen & Hallman [64]	1954	81	1 day	M	Bilateral	Finland
		82	18 days	M	?	
		83	22 days	M	Right	
		84	1 mo.	M	Bilateral	
Fournier & Pauli [65]	1955	85	11 days	?	Bilateral ?	France
		86	2 days	?	Left	
		87	16 days	?	Right	
Smith [66]	1955	88	13 days	M	Right	United States
Farquahr [67]	1956	89	2 days	?	?	England
Green & Blackford [68]	1956	90	1 mo.	M	Bilateral	United States
Tragis & Ellison [69]	1956	91	17 days	M	Right	United States
Tveterås & Rudström [70]	1956	92	8 days	F	Left	Sweden
Avery et al. [71]	1957	93	3 days	F	Right	United States
		94	Stillborn	F	Bilateral	
		95	5 days	?	?	
Kaufmann	1957	96	1 yr.	F	Right	United States

* In addition, I am aware of the following papers on renal vein thrombosis but was unable to obtain them: Rieke, 1940 [72]; Smith, 1954 [73]; Sugar and Levin, 1956,[74] and Balogh, 1956.[75] This tabulation does not include cases of the nephrotic syndrome in association with renal vein thrombosis. Reports by Vidal,[76] Derow et al.,[77] Becker,[78] Pollak et al.[79] and Feinerman et al.[80] indicate that only one such case has occurred in the neonatal period.



Age incidence of renal vein thrombosis.

On the basis of the collected cases, the Graph indicates the age distribution of renal vein thrombosis.

Table 2 summarizes the age distribution, indicating clearly that of a total of 96 cases of renal vein thrombosis in the pediatric age range 58 or 60% are under 2 months of age. However, 25 cases were aged 6 months or more.

In other words, 40% of all the cases of renal vein thrombosis reported in this century are beyond the age group generally considered in connection with this diagnosis.

Sex Distribution and Incidence of Unilateral and Bilateral Renal Vein Thrombosis.—The statement has been made in several publications on renal vein thrombosis that the left renal vein is affected more frequently than the right. In his review of 228 collected cases in all age groups, Abeshouse [10] reported 121 with unilateral thrombosis, the left renal vein being involved in 57 patients and the right, in 37. He states that the "frequent occurrence of the condition on the left side was particularly observed in adults and is probably explained by the peculiar anatomical relations of the left renal vein and the increased incidence of thrombophlebitis of the pelvic veins associated with pregnancy and pelvic inflammatory disease in the adult female." He makes no direct statement as to the incidence of involvement of the two renal veins in the pediatric case material.

In reviewing the literature for the age incidence of renal vein thrombosis we became interested in accumulating data to determine which vein was more frequently involved. Ninety-six cases in the pediatric age group were found in the survey of the literature since 1900. Sex was given for 82 cases; the side on which renal vein

TABLE 2.—*Age Incidence of Renal Vein Thrombosis*

Age	Cases			
	No.			%
First day	6			
2-7 days	11			
8-14 days	24	58		60
15-30 days	13			
1 mo.	4			
2 mo.	3			
3 mo.	4	13		
4 mo.	6			
5 mo.	--		38	40
6-12 mo.	6			
1 yr.	10			
2 yr.	3	25		
3 yr.	3			
Over 3 yr.	3			

TABLE 3.—*Distribution of Renal Vein Thrombosis According to Side Involved in Ninety-One Cases*

	Cases		
	No.	%	
Left	26	29	55
Right	24	26	
Bilateral	41	45	

TABLE 4.—*Sex Distribution of Renal Vein Thrombosis According to Side Involved in Eighty Cases*

	Right		Left		Bilateral		Total
	No.	%	No.	%	No.	%	No.
Females	4	10	14	34	23	56	41
Males	14	36	11	28	14	36	39
Both	18		25		37		80

TABLE 5.—*Patients with Renal Vein Thrombosis at Surgical Exploration (Twenty Cases)*

	Female		Male	
	No.	%	No.	%
Left nephrectomy	8	89	5	45
Right nephrectomy	1	11	6	55
Total cases	9	100	11	100

thrombosis occurred was stated in 91 cases, and both side and sex were reported in 80 instances.

In Table 3 are given the data from 91 cases in the pediatric age group. From this Table one must conclude that the two renal veins are equally involved in renal vein thrombosis. However, further analysis of the accumulated data reveals a significant difference in the distribution according to sex (in the 80 cases where sex and side involved are stated), as shown in Table 4.

In the 82 cases in which sex was stated, renal vein thrombosis occurred with equal frequency in the two sexes, 41 cases in females and 41 cases in males. From Table 4 it is evident that in males thrombosis occurs with essentially equal frequency on the right, on the left, and bilaterally. However, in females bilateral involvement is most frequently reported; when thrombosis is unilateral, it is found much more often on the left than on the right. In view of the fact that the information available from autopsied cases usually did not permit a decision as to which renal vein was originally involved in those cases with bilateral thrombosis, it is of interest to tabulate the cases which came to surgery with unilateral thrombosis. From Table 5 it is again evident that left renal vein thrombosis predominates in the female.

Comment

This review of cases of renal vein thrombosis recorded in the world literature indicates that only 60% of all cases occur in the neonatal period. It is clearly evident, therefore, that one must give as much consideration to this diagnosis in older infants and children as in neonates. The diagnosis of renal vein thrombosis must be kept in mind in all patients with macroscopic and/or microscopic hematuria, and if these findings are accompanied by a palpable mass in the flank the diagnosis must be considered above all others, since survival will largely depend on immediate exploration and nephrectomy. Although it is true that renal vein thrombosis is more likely to occur in the first two months of life, during which dehydration, infection, and the size of the blood vessels apparently predispose to its development, these conditions obviously are not peculiar to the newborn infant, as evidenced by the findings that 40% of all cases reported have been in infants and children beyond that age.

The information accumulated here shows clearly that the two sexes have equal incidence of renal vein thrombosis. However, analysis of the material as to sex and involvement of right or left renal vein in unilateral cases reveals significant differences. In boys we find equal distribution. Girls have a remarkably high incidence of left renal vein thrombosis. There appears to be a threefold increase over right renal vein thrombosis. This previously unreported finding receives further support in the analysis of the cases operated on for this condition. Again, there is a virtually identical number of cases on each side in boys. In girls left nephrectomy is reported eight times oftener than nephrectomy on the right side for renal vein thrombosis.

In the adult female the predominance of left renal vein thrombosis is well known and is attributed to the peculiar anatomical relationship between the ovarian and renal veins on the left, together with the factors involved in pregnancy, the puerperium, and pelvic inflammatory disease. Since these

factors are not present in infancy and childhood and since left renal vein thrombosis predominates in females in this age group as well, there would appear to be some other explanation for this predominance.

Summary

A case of renal vein thrombosis in a one-year-old infant is presented.

Despite a fairly extensive literature, modern textbooks devote little attention to the subject and stress its occurrence in the neonatal period.

A review of 96 pediatric cases in the world literature since 1900 reveals that 40% were in infants over 2 months of age.

This analysis shows no significant difference in sex distribution.

In males renal vein thrombosis is found with essentially equal frequency on the right, on the left, and bilaterally.

In females bilateral thrombosis occurs most frequently. When thrombosis is unilateral, it is found much oftener on the left than on the right side.

At present there is no explanation for these differences in occurrence.

Dr. Sydney S. Gellis gave advice and criticism in the preparation of this paper.

Department of Pediatrics, Boston University School of Medicine.

REFERENCES

1. Mills, W. G. Q., and Owen, T. K.: Renal Thrombosis Complicating Pink Disease: Cure by Nephrectomy, Arch. Dis. Childhood 28:301-302, 1953.

2. Holt, L. E., Jr., and McIntosh, R.: Holt Pediatrics, Ed. 12, New York, Appleton-Century-Crofts Company, Inc., 1953.

3. Paterson, D., and McCreary, J. F.: Pediatrics: A Symposium, Philadelphia, J. B. Lippincott Company, 1956.

4. Sheldon, W.: Diseases of Infancy and Childhood, Ed. 7, London, J. & A. Churchill, Ltd., 1955.

5. Slobody, L. B.: Survey of Clinical Pediatrics, Ed. 2, New York, McGraw-Hill Book Company, Inc., 1955.

6. Fanconi, G., and Wallgren, A. J., Editors: Textbook of Pediatrics, 1st English edition, New York, Grune & Stratton, Inc., 1952.

7. Glanzmann, E.: Einführung in die Kinderheilkunde, Ed. 2, Berlin, Springer-Verlag, 1946.

8. Potter, E.: Pathology of the Newborn and Fetus, Chicago, The Year Book Publishers, Inc., 1952.

9. Gross, R. E.: The Surgery of Infancy and Childhood, Philadelphia, W. B. Saunders Company, 1953.

10. Caffey, J.: Pediatric X-Ray Diagnosis, Ed. 3, Chicago, The Year Book Publishers, Inc., 1956.

11. Lassrich, M. A.; Prévôt, R., and Schäfer, K. H.: Paediatrischer Röntgenatlas, Stuttgart, Georg Thieme Verlag, 1955.

12. Nelson, W. E.: Textbook of Pediatrics, Ed. 6, Philadelphia, W. B. Saunders Company, 1956, p. 1094.

13. Brennemann's Practice of Pediatrics, Vol. 3, Hagerstown, Md., W. F. Prior Company, Inc., 1957, Chap. 32, p. 31.

14. Davison, H., and Levinthal, J. D.: The Compleat Pediatrician, Ed. 7, Durham, N. C., The Duke University Press, 1957, pp. 136 and 155.

15. Campbell, M., and Matthews, W. F.: Renal Thrombosis in Infancy, J. Pediat. 20:614-615, 1942.

16. Finkelstein, H.: Lehrbuch der Säuglingskrankheiten, Berlin, Springer-Verlag, 1925.

17. Pfaundler, M., and Schlossmann, A., Editors: Handbuch der Kinderheilkunde, Berlin, Springer-Verlag, 1924, Vol. 4, pp. 173 and 174.

18. Campbell, M.: Clinical Pediatric Urology, Philadelphia, W. B. Saunders Company, 1951.

19. Abeshouse, B. S.: Thrombosis and Thrombophlebitis of the Renal Veins, Urol. & Cutan. Rev. 49:661-675, 1945.

20. Giampalmo, A.: Sull' infarcimento renale emorrhagico del neonato, Atti. Soc. Ital. Pat. Roma, 1949.

21. Marshall, S., and Wapham, E.: Case of Bilateral Renal Infarction in Newly Born Infant, Lancet 2:428-429, 1936.

22. Milburn, C. L.: Hemorrhagic Infarction of the Kidneys in Infants, J. Pediat. 41:133-140, 1952.

23. Oppenheim, F.: Über den hämorrhagischen Niereninfarkt der Säuglinge, ein anatomischer Beitrag zu dem Kapitel der toxischen Cappillarwandschädigungen, Ztschr. Kinderh. 26:192-206, 1920.

24. Pontieri, F.: Su di un caso di infarto settico del rene sinistro in un neonato, Pediatria 44:159-165, 1936.

25. Fahr, T.: Über totale Nekrose beider Nieren nach Thrombose der Nierenvenen, thesis, Giessen, 1903.

26. Richardière, H., and Merle, É.: Thrombose de la veine rénale gauche chez un enfant de 15 mois, Ann. méd. et chir. inf. 14:426-429, 1910; Bull. Soc. pédiat. Paris 12:236-240, 1910.

27. Wirtz, A.: Thrombose der vena cava inferior, der venae renales und suprarenalis sinistra

mit tödlichem Ausgang bei einem 15-tägigen Säugling, Jahrb. Kinderh. *72*:467-471, 1910.

28. Heller, S.: Thrombose der beiderseitigen vena renalis bei einem Neugeborenen, Zentralbl. Gynäk. 47:1897-1899, 1923.

29. Petremand, S.: Beitrag zur Kenntnis der Nierenvenenthrombose bei Säuglingen, Klin. Wchnschr. *2*:2244-2245, 1923.

30. Schröder, K.: Über die Thrombose der Nierenvenen, Arch path. Anat. *262*:634-645, 1926.

31. Aschner, P. W.: Thrombosis and Thrombophlebitis of the Renal Vein, J. Urol. 17:309-327, 1927.

32. Färber, E., and Bussel, R.: Nierenvenenthrombose im Kindesalter, Monatsschr. Kinderh. 48:304-310, 1930.

33. Eilers, W.: Zur Kenntnis der primären unteren Hohlvenenthrombose im Säuglingsalter, Arch. path. Anat. *277*:248-255, 1930.

34. Nordwall, U.: Un Cas de thrombose, bilatérale de la veine rénale chez une nouveau-née, Acta. pædiat. 14:186-191, 1932.

35. Grüneberg, B.: Nierenvenenthrombose linkerseits, München. med. Wchnschr. *79*:1054, 1932.

36. Hepler, A. B.: Thrombosis in the Renal Veins, J. Urol. 31:527-546, 1934.

37. Behr, E.: Les Altérations morphologiques du rein dans la thrombose de la veine rénale (recherches anatomo-pathologiques et expérimentales), Arch. internat. méd. expér. 13:273-334, 1938.

38. Wegelin, C., cited by Behr.[37]

39. Hesse, B.: Ein Fall von Nierenvenenthrombose bei congenitalem Typhus abdominalis, Zentralbl. path. Anat. 75:196-197, 1940.

40. Perry, C. B., and Taylor, A. L.: Hypertension Following Thrombosis of the Renal Veins, J. Path. & Bact. 51:369-374, 1940.

41. Ungari, C.: Su di un caso di infarto emorragico bilaterale dei reni in un lattante (studio clinico e anatomopatologico), Lattante 11:55-70, 1940.

42. Barenberg, L. H.; Greenstein, N. M.; Levy, W., and Rosenbluth, S. B.: Renal Thrombosis with Infarction Complicating Diarrhea of the Newborn: Summary of 5 Cases, Am. J. Dis. Child. 62:362-372, 1941.

43. Koopmann, H.: Über Nierenvenenthrombose, Zentralbl. path. Anat. 82:88-90, 1944.

44. Morison, J. E.: Renal Venous Thrombosis and Infarction in the Newborn, Arch. Dis. Childhood 20:129-134, 1945.

45. Thurston, W. D.: Venous Thrombosis in the Newborn Kidney, Bull. Child. Hosp., Denver 1:97, 1947.

46. Lapointe, D.: Thrombose des veines rénales et infarctus du rein au cours des diarrhées épidémiques des nouveau-nées, Laval. méd. 12:582-586, 1947.

47. Sandblom, P.: Renal Thrombosis with Infarction in the Newborn: Two Different Forms, Acta pædiat. 35:160-167, 1948.

48. Freund, J., and Bick, G.: Über hämorrhagische Niereninfarkte im Kindesalter, Ztschr. Kinderh. 67:23-35, 1949.

49. Fallon, M. L.: Renal Venous Thrombosis in the Newborn, Arch. Dis. Childhood 24:125-128, 1949.

50. Smith, D. H., and Arey, J. B.: Thrombosis of the Renal Vein with Infarction of the Kidney, J. Pediat. 36:519-521, 1950.

51. McClelland, C. Q., and Hughes, J. P.: Thrombosis of the Renal Vein in Infant, J. Pediat. 36:214-227, 1950.

52. Feriozi, D.; Rice, E. C.; Burdick, W. F., and Troendle, F. J.: Thrombosis of the Inferior Vena Cava and Renal Veins with Hemorrhagic Infarction in Infancy, J. Pediat. 38:235-241, 1951.

53. Kobernick, S. D.; Moore, J. R., and Wiglesworth, F. W.: Thrombosis of the Renal Veins with Massive Hemorrhagic Infarction of the Kidneys in Childhood, Am. J. Path. 27:435-450, 1951.

54: Parry, E. W.: Unilateral Renal Vein Thrombosis Treated by Nephrectomy and Postoperative Heparin, Arch. Dis. Childhood 26:358-361, 1951.

55. Zuelzer, W. W.; Kurnetz, R., and Fallon, R.: Circulatory Diseases of the Kidneys in Infancy and Childhood: VI. Thrombosis of Renal Veins, Am. J. Dis. Child. 81:27-37, 1951.

56. Warren, H.; Birdsong, McL., and Kelley, R. A.: Renal Vein Thrombosis in Infants, J. A. M. A. 152:700-701, 1953.

57. DeCamp, P. T.; Ochsner, A., and Debakey, M.: Thrombo-Embolism in Children, Ann. Surg. 133:611-621, 1951.

58. Clark, C. P., and Pickup, J. P.: Hemorrhagic Infarct of the Kidney Treated by Nephrectomy, Arch. Dis. Childhood 28:302-303, 1953.

59. Clatworthy, H. W., Jr.; Dickens, D. R., and McClave, C. R.: Renal Thrombosis Complicating Epidemic Diarrhea in the Newborn, New England J. Med. 248:628-630, 1953.

60. Puccini, C.: L'infarcimento emorragico massivo del rene e della surrenale per trombosi venosa come causa di morte improvisa nell' infanzia, Minerva medicoleg. 73:1-16, 1953.

61. Stevens, R. C., and Tomsykoski, A. J.: Thrombosis of the Inferior Vena Cava and Renal Veins with Hemorrhagic Renal Infarction, J. Urol. 72:120-126, 1954.

62. Clinico-Pathological Conference, Clin. Proc. Child. Hosp. 10:83-86, 1954.

63. Ahvenainen, E. K., and Hallman, N.: Thrombosis of Deep Veins in Childhood: II. Thrombosis of the Renal Veins, Ann. paediat. Fenniae 1:105-115, 1954.

64. Buchtel, H., cited by Campbell,[10] p. 443.

65. Fournier, A., and Pauli, A.: Les Infarctus rénaux par thrombose des veines rénales chez le nouveau-né et le nourrisson, Nourrisson 43:229-243, 1955.

66. Smith, B. A., Jr.: Renal Vein Thrombosis in the Newborn, J. Urol. 73:765-773, 1955.

67. Farquhar, J. W.: Significance of Hypoglycemia in Newborn Infants of Diabetic Women, Arch. Dis. Childhood 31:203-211, 1956.

68. Green, A. J., and Blackford, L. M.: Renal Vein Thrombosis, J. M. A. Georgia 45:201-202, 1956.

69. Traggis, D. G., and Ellison, M. M.: Unilateral Renal Vein Thrombosis, J. Pediat. 48:229-231, 1956.

70. Tveterås, E., and Rudström, P.: Renal Thrombosis in the Newborn: Report of a Primary Case Successfully Treated by Surgery, Acta pædiat. 45:445-450, 1956.

71. Avery, M. E.; Oppenheimer, E. H., and Gordon, H. H.: Renal Vein Thrombosis in Newborn Infants of Diabetic Mothers, New England J. Med. 256:1134-1138, 1957.

72. Rieke, F.: Über Nierenvenenthrombose, insbesondere bei Kindern, Inaugural Dissertation, Hamburg, 1940.

73. Smith, B. A.: Renal Vein Thrombosis in the Newborn, in Proceedings of the North Central Section of the American Urological Association, Minneapolis, Burgess Publishing Company, 1954, p. 40.

74. Sugar, M., and Levin, S.: Renal Vein Thrombosis in Infancy, Harefuah 51:106-110, 1956.

75. Balogh, J.: Über eine in vivo diagnostizierte Nierenvenenthrombose des Neugeborenen, Zentralbl. allg. Path. 95:447-454, 1956.

76. Vidal: Bull. Soc. anat. Paris 29:321, 1854.

77. Derow, H. A.; Schlesinger, M. J., and Savitz, H. A.: Chronic Progressive Occlusion of the Inferior Vena Cava and the Renal and Portal Veins: With the Clinical Picture of the Nephrotic Syndrome; Report of a Case, with a Review of the Literature, Arch. Int. Med. 63:626-647, 1939.

78. Becker, A. H.: Intrarenal Vascular Thrombosis: Case Presenting Clinical Picture of Nephrotic Syndrome, Connecticut M. J. 18:21-25, 1954.

79. Pollak, V. E.; Mark, R. M.; Pirani, C. L.; Shafter, H. A., and Muehrcke, R. C.: Renal Vein Thrombosis and the Nephrotic Syndrome, Am. J. Med. 21:496-520, 1956.

80. Feinerman, B.; Burke, E. C., and Bahn, R. C.: The Nephrotic Syndrome Associated with Renal Vein Thrombosis, J. Pediat. 51:385-391, 1957.

Ataxia, Telangiectasia, and Sinopulmonary Infections

A Syndrome of Slowly Progressive Deterioration in Childhood

WILLARD R. CENTERWALL, M.D., and MELBA M. MILLER, Ed.D., Los Angeles

Two case histories including one autopsy are presented here of children with such a similar and unusual course of disease that it appears to be a syndrome. These two children are unrelated, and both have been patients at the State School for Cerebral Palsied Children, Southern California. The older child, who recently died as a result of his disease at the age of 12¾ years, had been under close observation since 4½ years of age. A third case is also included which was originally described by Madame Louis-Bar in the Swiss literature in 1941.[1] We believe that her case may be the first description of this syndrome in the medical literature.

The major features of the syndrome are slowly progressive ataxia, progressive symmetrical scleral-cutaneous telangiectasia, and increasing chronic and recurrent lung infections.

Submitted for publication July 29, 1957.

From the Department of Pediatrics, College of Medical Evangelists School of Medicine (Assistant Clinical Professor, Dr. Centerwall), Los Angeles, and the State School for Cerebral Palsied Children of Southern California (Superintendent, Dr. Miller), Altadena, Calif.

Report of Cases

CASE 1.—A Caucasian boy was first referred to the State School for Cerebral Palsied Children, Southern California, on Feb. 24, 1949, at the age of 4 years 5 months. The major complaints were slowly progressive unsteadiness of gait and clumsy use of the hands of approximately two and one-half years' duration. Telangiectasia of the sclerae had been present for nearly one and one-half years.

Infancy had been considered normal. He sat alone at 7 months (Fig. 1), stood with support at 10 months (Fig. 2), and said first words at approximately 14 months of age; however, he did not walk until 2 years of age and then with a peculiar unsteadiness which persisted and progressed. He was fairly well bowel trained at 15 months and bladder trained at 3 years; however, he continued to have occasional wetting accidents. He did not feed himself until 3 years of age. Photographs as early as 18 months show the first insidious signs of drooping, hunched-over posture with mouth agape (Fig. 3). In retrospect, the parents believe that he did not sit as well as he should have during infancy and that clumsy use of the hands dated back to the first year of life.

Examination at the Cerebral Palsy School in 1949 revealed a small well-nourished right-handed Caucasian boy of 4½ years who was alert, friendly, and cooperative. He had a moderately unsteady gait with veering to either side and a slightly hunched-over posture with a tendency to tilt his

Fig. 1 (Case 1).—Patient sitting alone at 7 months of age.

Fig. 2 (Case 1).—Patient standing with assistance at 10 months of age.

Fig. 3 (Case 1).—Patient at 18 months of age, demonstrating the first insidious signs of drooping, hunched-over posture with mouth agape.

Fig. 4 (Case 1).—Patient at 7 years of age. Posture is abnormal, but nutrition is still good. Background lines are 6 in. apart.

head to the side. He was clumsy and slow with hand function (could dress himself except for buttoning and lacing). Mentality was grossly normal. Speech was clear but lacking in volume and strength. Hearing was intact, and vision was 20/50 in each eye. There was a prominence of blood vessels on the exposed areas of the sclerae. There was a watery nasal discharge and some injection of the nasal septum. Heart, lungs, and abdomen were unremarkable; vital signs were normal. The diagnosis was cerebral palsy, quadriplegic ataxia versus athetosis.

Five of the last eight years of his life were spent at the State School for Cerebral Palsied Children where one of us (M. M.) was able to observe closely the steady progression of his disease. The boy was at home for the last two and one-half years of his life but was returned for periodic evaluations. The ataxia slowly progressed, with associated generalized weakness, and by 8½ years of age he was almost completely confined to a wheel chair, walking only 10 to 20 ft. per day and requiring a football helmet for head protection. Food was spilled oftener, and speech had become slurred. By 10 years of age a bilateral nystagmus and a bilateral intention tremor had been noted. The sensory system apparently was unimpaired (i. e., taste, smell, touch, position, pain, temperature, pressure). Frequently over the years he had been thought of as "lazy" and "not trying hard enough." It gradually became apparent that this was part of his disease—that he was slow even when he knew what was expected and wanted to do it. Diurnal enuresis and occasional nocturnal enuresis persisted. Hearing (audiogram tests) remained normal except for a transient loss secondary to otitis media.

Meanwhile the amount of telangiectasia slowly increased. The external ears, the "V" of the neck, and, more recently, the antecubital regions became symmetrically involved (Plate, Figs. 11-14).

He had a watery nasal discharge most of his life, and at about 7 years of age he developed a chronic cough which persisted thereafter. This age of onset of his chronic lung condition seemed to coincide with the acceleration of his general downhill course and accompanying severe weight loss (Figs. 4-10). After CA 7-6* he was hospitalized 15 times for chronic bronchitis, chronic sinusitis, chronic pneumonia, and removal of tonsils and adenoids. When examined at CA 12-9, three weeks before his death, he appeared to be almost terminal, with severe diffuse pneumonia and emaciation. It is noted from Figure 10 that his social quotient was fairly stable between 85 and 90 up through CA 7-9. Thereafter it rapidly and steadily decreased.

Memory, comprehension, and concentration had always been adequate, and various tests scored within normal range of intelligence; e. g., at CA

*CA means chronological age or actual age; i. e., CA 7-6 means an age of 7 years 6 months.

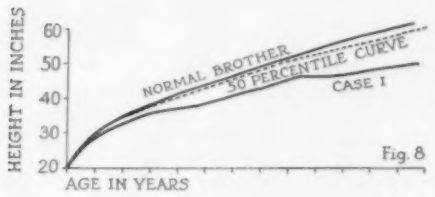
Fig. 5 (Case 1).—Patient at 12 years 7½ months of age. He has become extremely emaciated and is unable to stand without support. Note the minimal gain in stature over the five and one-half years.

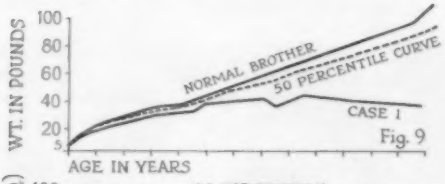
6

Fig. 6 (Case 1).—"Drawing of a man" at 6 years of age. Drawing time: one-half hour. Note the use of details such as buttons, pocket, and cap.

7

Fig. 7 (Case 1).—"Drawing of a man" at 12 years 7½ months of age. Drawing time: more than one hour. Note the deterioration in drawing skill and loss of details over the six and one-half years.





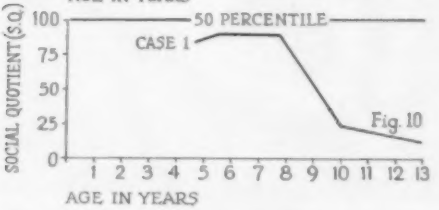


Fig. 8 (Case 1).—Height curve as compared with that of the older normal brother and that of the average American boy. At CA 12-9, Patient 1 is the height of an average 7½-year-old boy.

Fig. 9 (Case 1).—Weight curve as compared with that of the older normal brother and that of the average American boy. Note that this small boy's weight and height were in good proportion until after approximately 7 years of age. Weight at CA 12-9 is average for 4-year-old boy.

Fig. 10 (Case 1).—Social quotient (SQ) scores on the Vineland Social Maturity Scale as compared with the expected normal of 100. The physical and social deterioration which started in the early school years coincided with the onset of chronic lung infections.

4-9, MA † 5-1, IQ 107; at CA 7-0, MA 7-2, IQ 102. Motor lag in relation to a mental task had always been a pertinent characteristic of this boy. One did not need to repeat a question; for he would keep it in mind for half an hour if necessary. More recently there was probably some mental deterioration too, but major regression was lacking. At CA 12-9 he was using the vocabulary of a young child of about 5 and conversed chiefly with his mother. He did relate experiences to her and was able to tell a story with logical sequence. Social regression is observable before mental regression in a deteriorating process. His scores on the Vineland Social Maturity Scale were, therefore, especially significant (Fig. 10).

There were numerous other tests and examinations over the course of years, including negative urinalyses, with a specific gravity persistently over 1.020; hemoglobin range 11.5 to 13.6 gm. per 100 cc.; WBC range 3400 to 23,150, with differential counts at the times of high total counts consistent with bacterial infections and occasionally an inadequately explained eosinophilia (eosinophils ranging from 7% to 15%); total serum protein (CA 12-9) 5.8 gm. per 100 cc. (A/G ratio, 3.1:2.7), γ-globulin 4% of total (normal 11% to 19%), and an electrophoretic pattern characteristic of an acute inflammatory process; chest x-rays (CA 7-11) showing slight prominence of vascular markings; bronchiogram (CA 7-11), bilateral diffuse mild bronchiectasis; chest x-ray (CA 12-9), bilateral advanced bronchopneumonia; skull x-ray (CA 2-3), normal; tuberculosis patch tests (CA 4-7, 6-7, and 9-1), negative; stool trypsin (CA 8-0),

† MA means mental age; i. e., MA 5-1 means mentally like an average 5 years-1-month-old child.

normal; duodenal drainage for trypsin (CA 9-2), normal; Kahn test (CA 3-4), negative; EEG (CA 7-9), diffusely abnormal with disorganized activity in all leads and EEG (CA 9-6), too little organization and too low amplitude but no clear-cut abnormalities; NPN (CA 9-6), 32 mg. per 100 cc.; lumbar puncture (CA 12-9), normal pressure, 1 monocyte, protein 20 mg. per 100 cc., and sugar 72 mg. per 100 cc.; urinary total porphyrins and porphobilinogen levels not elevated, phenylpyruvic acid absent, urinary amino acid nitrogen (CA 12-9) 52 and 37 (av. 44) mg. in 24 hours (normal control, 40 mg.); respiratory vital capacity (CA 12-9), 460 cc., or 16% of normal; cultures of nasopharynx and tracheobronchial tree, Micrococcus (Staphylococcus) pyogenes var. aureus, coagulase-positive.

Although he received almost continuous medical care during the last eight years of his life, nothing seemed to change the course of his illness other than antibiotics to prolong life itself.

Other past history: Pregnancy was normal and birth was full-term, spontaneous, and uneventful. Birth weight was 7 lb. 7 oz. He was bottle-fed, with no initial problems. Late self-feeding and decreasing appetite were part of his general course. He had uncomplicated measles and chickenpox at 2 and 3 years, respectively.

Family history: Mother (German-French-Dutch) was 24 years old when the patient was born. Father (Welsh) was 33. This boy was the second of the only two pregnancies, and the older brother, now CA 14-9, has been perfectly normal. At CA 12-6, this brother was 1 ft. taller and 63 lb. heavier than our patient was at CA 12-9 (Figs. 8 and 9). Other family history is noncontributory.

Physical examination at CA 12-9 revealed a small, severely wasted, thin-chested boy who was wheelchair-bound, standing only briefly with support (Fig. 5). Height was 50¼ in.; weight, 37 lb.; head circumference, 20⅛ in.; chest circumference, 23 in.; B. P. 82/60; respirations, 35 to 40 per minute. There was a marked ataxia of the upper extremities, a mild to moderate intention tremor, and bilateral nystagmus. Deep reflexes were hypotonic; superficial reflexes, normal; Babinski and clonus, absent. Sensory system was grossly intact. Plantar arches were normal. He was friendly and cooperative, talked minimally with a slow soft voice, and was very slow to initiate any motion. If his hands were pushed in the right direction, the inertia would be broken somewhat, and he would procede slowly with his task.

A symmetrical telangiectasia (Plate, Figs. 11-14) was noted on the exposed areas of the sclerae (with some extension onto the suborbital skin and bridge of nose), the external ears (with some extension onto the posterior auricular scalp), the "V" of the neck, and the antecubital regions. The fundi, auditory canals, tympanic membranes, and mucous membranes were spared. The nasal septum was slightly hypervascular—believed secondary to chronic discharge. A 2×3 cm. café au lait spot was noted at the angle of the jaw on the right side.

Occasionally he was racked with a deep nonproductive cough; his chest was dull to percussion, and sticky, moist, medium rales were heard throughout.

He was admitted to the hospital in critical condition. Despite the use of antibiotics, oxygen, and parenteral fluids, he died two weeks later of overwhelming chronic pneumonia. Toward the end, the telangiectasia became dark red and there was some swelling of the feet and eyelids. He remained oriented until the last day or two of life.

An autopsy was performed on the embalmed body, giving the following findings: Obvious gross abnormalities of internal organs were limited largely to the lungs, which showed puckered areas of induration on the surface and scattered indiscrete areas of consolidation on cut section. The upper lobes seemed more severely involved than the lower lobes. The mucosa of the upper bronchi appeared diffusely thickened, and the distal bronchi were dilated and filled with yellow-green purulent material.

The brain appeared fairly normal grossly. The pituitary was not examined. Gross vessel evaluation was difficult, because blood had been washed out of the vascular channels with the embalming fluid. Cut sections were likewise grossly normal. However, on microscopic section, the brain showed significant pathology. These findings include some thickening of the leptomeninges; large meningeal venules; some free red blood cells in the meningeal spaces; scattered loss of pyramidal cells of the

Patient 1 at 12 years 9 months of age.

Fig. 11.—Note the telangiectasia, the generalized wasting, and the tilt of the head. He is wheelchair-bound.

Fig. 12.—Demonstration of blanching of telangiectasia on the "V" of the neck by means of glass slide.

Fig. 13.—Telangiectasia on the external ears and extending onto the postauricular scalp.

Fig. 14.—Close-up view showing vascular network on the sclera.

Patient 2 at 7 years 9 months of age.

Fig. 15.—Note the telangiectasia on the collar region and "V" of the neck. Both strabismus and pleasing personality are apparent. Nutrition is good at this age.

Fig. 16.—Close-up view of telangiectasia in the antecubital region.

Fig. 17.—Close-up view of telangiectasia on the external ear.

Fig. 18.—Telangiectasia of the sclerae, demonstrating the sparing of the unexposed regions.

Figure 11

Figure 15

Figure 12

Figure 16

Figure 13

Figure 17

Figure 14

Figure 18

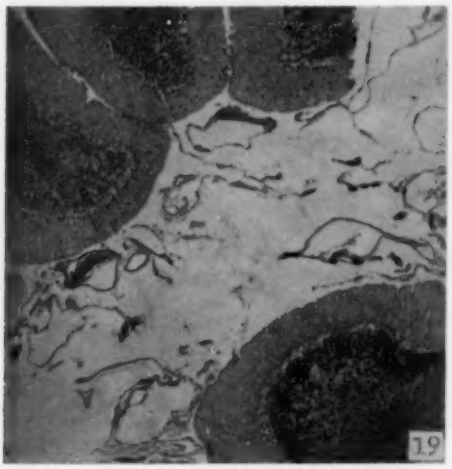


Fig. 19 (Case 1).—Cerebellar leptomeninges showing many much-enlarged thin-walled venules. Hematoxylin and eosin; × 30.

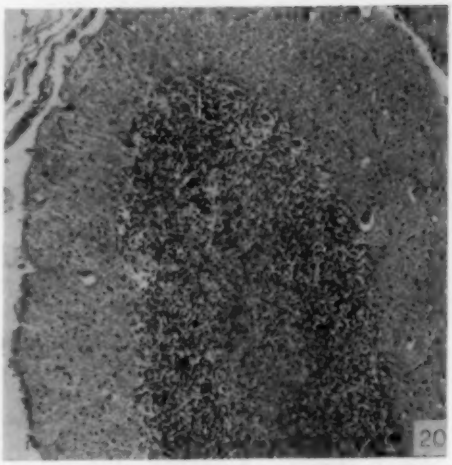


Fig. 20 (Case 1).—Cerebellar folia, showing degenerative changes in the granule-cell layer. Loss of Purkinje cells and pyknotic changes in remaining cells are also indicated. Hematoxylin and eosin; × 75.

frontal cortex, especially of the central gyri; irregular large venules of the frontal centrum, and unusually large venules in the parietal lobe and in the dentate nucleus. The substantia nigra showed some loss of pigmented cells, and tissue about the cells had a peculiar fenestrated appearance (early status spongiosus). The venules of the inferior olivary nucleus may have been slightly larger than average; however, the venules of the basal leptomeninges were very conspicious by their increased size. The venules in the cerebellar meninges also were somewhat enlarged and thin-walled, with some folding and tortuosity. The cerebellar cortex in some areas appeared to be pale, indicating a loss of parenchymal elements—an irregular loss of Purkinje cells with pyknotic changes seen in most of the remaining cells and a thinning of the granule-cell layer. Venules in the cerebellar white matter showed variable degrees of enlargement. Cells in the dentate nucleus were seen to be undergoing pyknotic change.

Microscopic examination of the lungs revealed dilated bronchioles, with some ulceration of epithelium and with walls thickened by inflammatory-cell infiltration of all types but predominantly by lymphocytes and plasma cells. Other

Fig. 21 (Case 1).—Cluster of enlarged venules in cerebellar white matter. Hematoxylin and eosin; × 49.

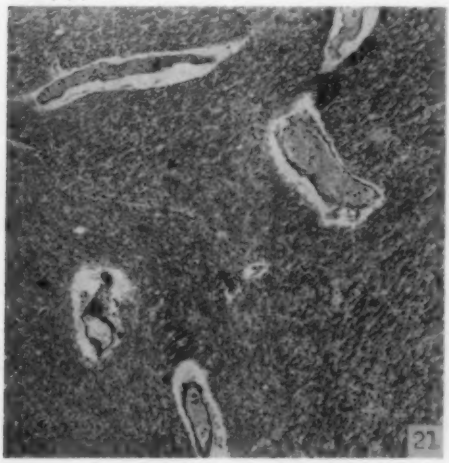
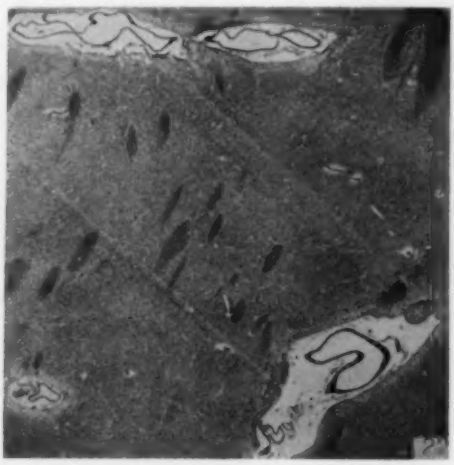


Fig. 22 (Case 1).—Enlarged tortuous thin-walled venules in lenticular nucleus. Hematoxylin and eosin; × 20.



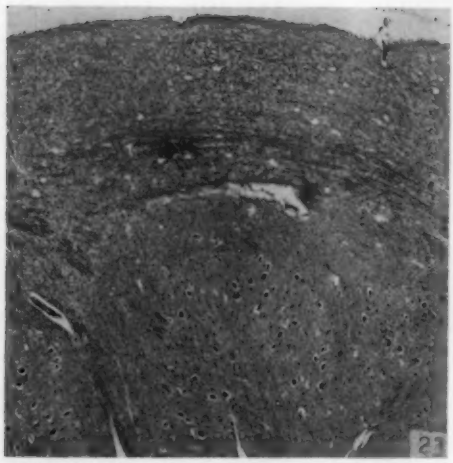


Fig. 23 (Case 1).—Section through dentate nucleus, showing pyknotic changes in nerve cells. Hematoxylin and eosin; × 50.

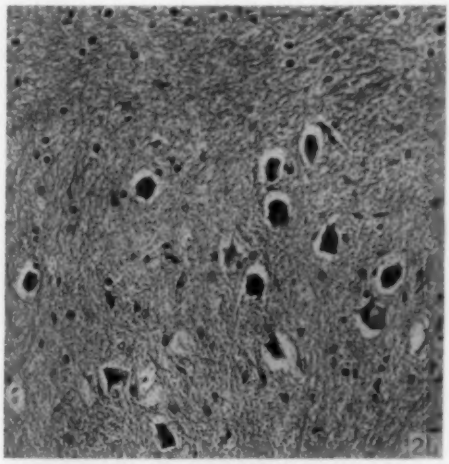


Fig. 24 (Case 1).—Higher-power magnification of the same view. Hematoxylin and eosin; × 250.

sections of the lung revealed the alveoli to be filled with polymorphonuclear cells and, in some sections, a hyaline stringy material suggestive of aspiration. Vascular abnormalities could not be demonstrated in the lungs.

The liver weighed about 1000 gm. and appeared grossly unremarkable. Microscopic study, however, revealed diffuse fatty degeneration of liver cells and portal area infiltration with mononuclear cells.

Photographs of some abnormal findings in the brain, lungs, and liver are included in Figures 19 through 26.

Case 2.—An 8-year-old Caucasian boy was first seen in the Cerebral Palsy Diagnostic Clinic ‡ on Jan. 25, 1957. He was thought to be normal until approximately 2½ years of age. At that time, his walking became unsteady. Because of a slow progression of this symptom, he was seen in another hospital clinic at 5 years of age. Telangiectasia of the sclerae and ears were noted at that time. The mother recalled that this began in the eyes

‡ State Cerebral Palsy Diagnostic Clinic, White Memorial Hospital, College of Medical Evangelists, Los Angeles.

Fig. 25 (Case 1).—Section through the lungs, showing thick-walled bronchus with denuded epithelium and adjacent exudate-filled alveoli. Hematoxylin and eosin; × 22.

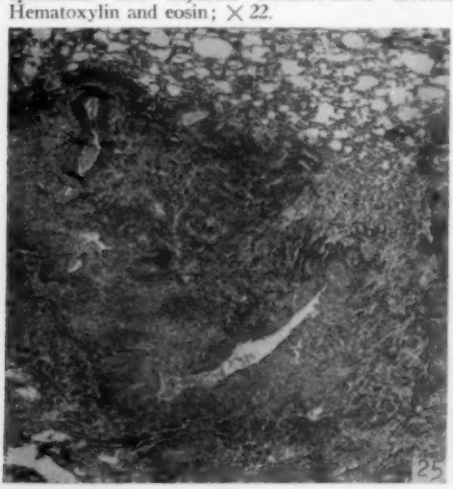
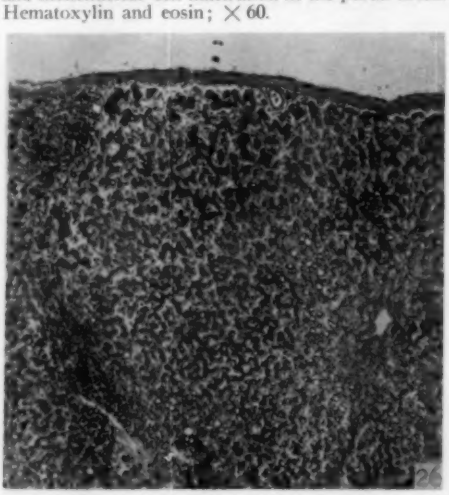


Fig. 26 (Case 1).—Section through the liver, showing loss of paryenchyma, fatty degeneration, and mononuclear-cell infiltration in the portal areas. Hematoxylin and eosin; × 60.



when he was about 3 years of age. An EEG and roentgenograms of the skull were normal.

Since 5½ years of age, there has been an acceleration of the unsteadiness and incoordination. Much of his life he has had a watery nasal discharge, but at about 5 to 6 years of age he had the onset of a chronic cough and lung infection which has persisted more or less to the present. An internal strabismus dates from approximately this same age, and since then the telangiectatic areas have also been increasing more rapidly.

He was referred to the Cerebral Palsy Clinic for further evaluation at 7½ years of age. Examination at that time revealed the following: B. P., 102/50; weight, 47¾ lb.; height, 48¼ in.; head circumference, 20 in. The patient was a fairly slender, smaller than average 7½-year-old Caucasian boy who was quiet yet alert, cooperative, and friendly. He had hazel-green eyes, brown hair, and an average Caucasian complexion. There were superficial fine red vessels which blanched on pressure on the external ears, lateral sides and "V" of the neck, and antecubital regions (Plate, Figs. 15-17). The auditory canals, tympanic membranes, mucous membranes, and fundi were not involved. There were two small dark brown nevi on the neck and chest. No café au lait areas were noted. The eyes showed dilation of the superficial vessels of the sclerae, with sparing of the areas covered by the lids (Plate, Fig. 18). There was an internal strabismus of the right eye, extraneous extraocular movements without true nystagmus, and normal fundi. Visual acuity was slightly impaired; photophobia was absent. The nose and throat were normal in appearance. There was no lymphadenopathy. Heart and abdomen were normal. Chest and lungs were normal to inspection and percussion. There was a deep slightly moist cough, and the voice was soft and slightly nasal. Auscultation of the lungs revealed musical-type medium rales in the posterior bases bilaterally.

Neuromuscular examination revealed a semipropulsion type of gait with veering to the sides, especially to the right. The left hip was slightly elevated, and there was pronation of the feet bilaterally. Posture at rest showed hips bent forward, shoulders bent forward, and leaning of the head to the right. He had mild incoordination and tremor with writing and fine movements and was not able to tie a knot. He had some past-pointing with the left upper extremity. The Romberg test was equivocal. Muscle strength was intact, and there was no fasciculation of the tongue. Deep tendon reflexes were very hypotonic, and superficial reflexes were normal. Tests for stereognosis, adiadochokinesis, Babinski reflex, and position sense were normal. Plantar arches appeared normal. He seemed to be a happy, affectionate, and obedient boy.

Family history: Mother (Jewish) was 22 years old when the patient was born. Father (Mexican) was 42. He was the second of two siblings. The other child, aged 9 years, is a half-brother by the same mother. This brother has a fairly severe behavior problem. The mother has been a known diabetic since 11 years of age, and three years ago (five years after the birth of our patient) she had poliomyelitis, resulting in right hemiparesis. The father and half-brother are living and well.

The patient was born by cesarean section, performed with use of spinal anesthesia at 35 weeks because his mother had toxemia of pregnancy (without convulsions). Birth weight was 8 lb. 3½ oz., and birth length was 19 in. There were no postpartum difficulties. He held up his head at 5 months, walked alone at 18 months, and spoke his first words at 22 months. He seemed generally slow and had difficulty with feeding himself and dressing. He seemed ambidexterous in early childhood but has become right-handed. He was toilet trained at 1½ years but still wets his pants two or three times a week while at play. He rode a tricycle at 5 years of age. He has always been bashful with strangers but gets along well with both children and adults. He is at present a low average student in the second grade of the public school.

He had an accident which consisted of falling from the car at 3 years of age. He was not unconscious; he had no associated signs or symptoms, and no treatment was necessary. He had uncomplicated three-day measles at 4 years of age. He has worn eye glasses for myopia since the age of 5½ years.

In the six-month interval since he was first seen he has become significantly more unsteady, requiring a helmet for protection. The telangiectatic areas have spread further in the neck region and are seen now for the first time in popliteal areas. He now has definite slight bilateral horizontal nystagmus and a flickering of the eyelids upon initiation of lateral gaze. Part of this time has been spent at the State School for Cerebral Palsied Children, Southern California. Various tests and observations during this interval have revealed the following findings: EEG with generalized disorganization of wave pattern; normal chest x-ray; Bender Visual-Motor Gestalt Test indicating evidence of organic brain damage, Stanford-Binet (Form L) at CA 7-10 giving MA of 7-0, or IQ 89 (he also was noted to be slightly slower than average in initiating responses); audiogram was essentially normal, with slight loss of acuity in left ear; visual acuity, minimally reduced. Pneumoencephalogram showed normal skull with slight diffuse symmetrical enlargement of the lateral ventricles. The fourth ventricle appeared to be of normal size; there was no evidence of

Fig. 27 (Case 2).—Vertebral arteriogram, showing some clumping of dye in the deeper vessels of the cerebellum. See adjacent drawing for orientation.

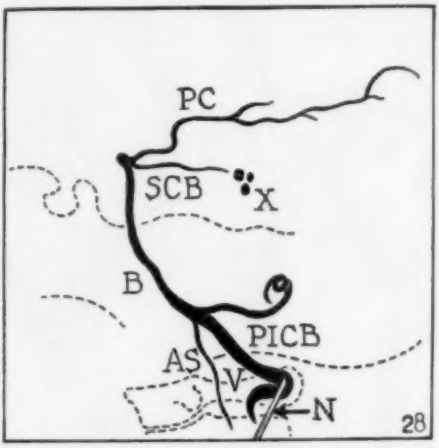


Fig. 28 (Case 2).—Diagram of findings of vertebral arteriogram. *N*, needle; *V*, vertebral artery; *AS*, anterior spinal artery; *B*, basilar artery; *PICB*, posterior inferior cerebellar artery; *X*, clumping of dye in deep vessels of cerebellum. This is not present on plain films of the skull.

cerebellar atrophy. Vertebral arteriograms demonstrated fairly well the basilar artery, the posterior cerebral arteries, and the superior and posterior cerebellar arteries. There was some clumping of dye in the internal circulation of the right cerebellar hemisphere, suggesting dilatation of the involved vessels (Figs. 27 and 28). A battery of other tests was performed: analysis of the blood, serum, cerebral spinal fluid, urine, and sweat. All these were within normal limits, including an electrophoretic pattern of serum proteins and skin tests for tuberculosis and coccidioidomycosis.

In addition, he was given a day's exposure in the sunshine, with resultant minimal (not considered significant) increase in unsteadiness. The telangiectasia transiently became brighter red. Also, a specific area of the abdomen and one ear were subjected for brief periods daily for three weeks to the ultraviolet rays of a sun lamp. The areas became well-tanned but showed no evidence of telangiectasia of the abdomen or increase in telangiectasia of the ear. It would appear that if sunlight exposure has any effect on the telangiectasia of this syndrome the changes are more subtle and long-term than could be demonstrated in this brief experiment.

The following is an abbreviated free translation from the original French.[1] This case is included because of the similarity to Cases 1 and 2 and because we believe that this may be the first description of this syndrome in the medical literature.

Case 3.—Louis van A. was first seen in consultation in October, 1940, at the age of 9 years. He had seemed perfectly normal during infancy except for some strabismus. He first walked at 15 months. At 2 years the first telangiectasia appeared. At 3 years he was noted to have developed a tendency to fall backward, especially when trying to sit down. Speech was slightly delayed and indistinct but within normal limits for his age. Thereafter all features progressed slowly, until whooping cough at 6 years of age seemed to accelerate the steady progression. Speech was definitely weak; more falling occurred, and involuntary jerking, especially of the right shoulder, was noted.

At 9 years of age he was a very blond well-nourished boy, mildly obese (especially the legs), with slight genital retardation. He stood bending his trunk forward with drooping of the shoulders and tilting of the head to the left. He had small tic-like movements of the neck, shoulders, and peribuccal musculature. The Romberg test was positive. He had no vertigo, but he vomited and had nystagmus with irrigation of the auditory canal. There was an ataxic gait with a tendency to fall to the right. There were hypotonia of the forearms and hands, feeble deep tendon reflexes, normal abdominal reflexes, absent Babinski reflexes, and a slight intention tremor. Writing was slow and trembling; there was no adiadochokinesis. Speech was weak and slow.

The external ears and the exposed areas of the sclerae showed bilateral symmetrical telangiectasia. The fundi were normal. A convergent strabismus was present (from infancy). A lattice-work telangiectasia which blanched on pressure was present symmetrically over the epitrochlear and

adjacent regions of the arms and portions of the lower legs and dorsa of the feet. There were fern-like café au lait spots on the back, chest, and posterior and anterior aspects of the thighs.

Mental status showed definite "insufficient scholastic attainment" (no specific tests were mentioned).

Follow-up examination one-half year later revealed adiadochokinesis and extention of the telangiectasia to involve the unexposed sclerae and the pretibial regions.

The father has café au lait spots and had mild transient speech and gait retardation in his youth.

Comment

Three cases have been presented here which are remarkable for the similarity of eye, skin, and central nervous system involvement. All three have a slowly progressive cerebellar ataxia associated with a progressive symmetrical telangiectasia. The two cases which we observed are practically identical. The third case, described by Louis-Bar, is strikingly similar. (It would seem reasonable to suspect the presence of this syndrome in any preschool or school-age child who presents with symptoms of ataxia and aseptic "conjunctivitis".)

Of particular interest in these cases is the problem of whether or not the children are mentally retarded. Careful testing reveals that our two children have IQ's within the normal range, although scholastic and social achievements are considerably reduced. We think that this reduction is due mainly to neuromuscular disability. The two drawings done by Case 1 (Figs. 6 and 7) demonstrate the increasing severity of the physical handicap. Without careful evaluation this handicap might easily be interpreted to be mental deficiency. Therefore, we wonder if the "insufficient scholastic attainment" of the Louis-Bar case is actually mental deficiency.

The peculiar distribution of the telangiectasia on symmetrical exposed areas of the body and the simultaneous slow progression of these lesions and cerebellar ataxia have caused us to speculate about the possible deleterious or modifying influence of sunlight on this syndrome. We wondered whether it was more than pure coincidence that our two cases of this apparently rare syndrome should both be living in sunny Southern California. We wondered if possibly this same disease in a less sunny climate might manifest less of the oculocutaneous telangiectasia. Certain recognized photosensitive conditions are known to have associated central nervous system symptoms: In Hartnup § disease,[2] recently discovered in England, direct sunlight results in a pellagra-like rash on the exposed areas of the skin and associated cerebellar ataxia. The ataxia is reversible, but there appears to be a slowly progressive mental retardation. These cases have a persistent aminoaciduria. Our patients were checked and found to have normal total amino acid excretion. Although we do not have a solution, we feel that a metabolic disturbance may well be the basic defect in the syndrome. Further investigation along this line would seem to be indicated. It is interesting that in Hartnup disease and in our cases infections seem to play an accentuating role. Kaposi's disease (xeroderma pigmentosa)[3] is a photosensitive disease in which senile skin changes, including telangiectasia, occur on the exposed areas. This is a progressive and fatal disease which may have such associated central nervous system symptoms as epilepsy, mental deficiency, and deafness. Congenital telangiectatic erythema,[4] a syndrome reported in 1954, is manifested by erythematous telangiectatic plaques in the butterfly area of the face, a bullous erruption of the lips, numerous café au lait spots on the trunk, and dwarfism. The skin lesions began to appear at approximately 2 years of age, and it is believed that hypersensitivity to sunlight may possibly play a minor role in the course of the disease. The dwarfism is more pronounced than in our cases, and there is no evidence of ataxia or other neuromuscular symptoms in these patients. In Rendu-Osler-Parkes Weber disease[5-7] (hereditary hemorrhagic telangiectasia) the vascular lesions (minute reddish purple spots) can be found almost anywhere, including the

§ Surname of the involved family.

eyes, brain, and lungs. However, the mucous membranes are most frequently favored, and in our cases the mucous membranes were spared. Repeated hemorrhages are common, and progressive ataxia is not a part of the syndrome.

Of all the ataxia syndromes we reviewed, it appears that von Hippel-Lindau [8,9] disease (cephaloretinal angiomatosis) is most closely related to our cases. In this disease there is an onset in childhood or early adulthood of progressive retinal and cerebellar angiomata with associated progressive vision loss and ataxia. Arteriograms sometimes demonstrate vascular lesions which are amenable to surgery. It was with such hopes that one of our cases was studied by vertebral arteriogram. There appeared to be some clumping of dye in the smaller deep cerebellar vessels but not of a size or location suitable for surgery. These findings were borne out later when the other boy died and was autopsied.

It is fairly reasonable to correlate, as part of one process, the oculocutaneous with the central nervous system telangiectasia. The chronic degenerative changes seen in the cerebellum are adequate to explain the progressive ataxia. It is more difficult to correlate the extensive brain-cell damage with the vascular phenomena. That all this could be secondary to stasis anoxia on a vascular basis is at best problematical. We were unable to demonstrate a vascular basis for the chronic and severe respiratory problem, and we could not demonstrate that this was due to a depression of protective antibodies. One child had a low γ-globulin level, which we felt was secondary to the inflammatory process. We did not investigate for the presence of abnormal γ-globulins. Although we feel that the respiratory problem is part of the syndrome, at this time we are unable to explain satisfactorily just how this might be related to the skin or central nervous system aspects. Pneumonia is the terminating complication of this syndrome, and this may account in part for the apparent scarcity of cases prior to the age of antibiotics.

Each of the above-compared syndromes and most of the known progressive ataxias are heredofamilial.[10,11] This would lead one to speculate that this syndrome may also be heredofamilial. By both clinical and pathology findings, this syndrome is best classified with that group of disorders known variously by such terms as the neuroectodermal dysplasias,[12] congenital ectodermoses,[13] and phakomatoses.[14] These include certain syndromes which involve the skin, eye, and central nervous system, i. e., cephaloretinal angiomatosis (von Hippel-Lindau disease), cerebral angiomatosis (Sturge-Weber syndrome), neurofibromatosis (von Recklinghausen's disease), and tuberous sclerosis (Bourneville's disease). Following these examples of labeling by pathology and by proper names, it would seem reasonable to call this syndrome "cephalo-oculocutaneous telangiectasia" (Louis-Bar syndrome). It makes an interesting finis to note that Ludo van Bogaert who, in 1940, referred that first case of "cephalo-oculocutaneous telangiectasia" to Madame Louis-Bar is the same person who, five years earlier, had coined the term neuroectodermal dysplasias.

Summary

Two cases are presented of what appears to be a definite syndrome—i. e., onset in late infancy of slowly progressive ataxia and slowly progressive symmetrical scleral-cutaneous telangiectasia and onset of chronic progressive lung disease at school age. A very similar case reported in the Swiss literature of 1941 is compared to these cases.

The autopsy findings of one case are presented. The enlarged venules and chronic degenerative cell changes seen in the cerebellar region are adequate to explain the progressive ataxia. Similar pathology was detected to a smaller degree in the cerebrum. Vascular anomalies were not demonstrated in the lungs.

The syndrome is compared briefly to other known syndromes manifesting chiefly telangiectasia or ataxia or both.

Siegried A. Centerwall, M.D., and Ewald R. Lonser, M.D., assisted in proof reading and translations. E. E. Pautler, M.D., performed the autopsy and supplied us with tissues for study, and Abraham T. Lu, M.D., reviewed with us the microscopic slides of the various organs of the body. Cyril B. Courville, M.D., Neuropathologist and Professor of Neurology at the College of Medical Evangelists, performed both the gross and the microscopic examination and analysis of brain tissue as reported in this article. The successful and diagnostically important vertebral arteriogram was performed by Marvin A. Korbin, M.D., utilizing his own special technique.[15] Mr. Edward Hamilton and Mr. Wilbur Rich, of the Visual Education Department of the College of Medical Evangelists, were responsible for the majority of photographs used in this article. Graphs and diagrams are by Mrs. Lucille C. Innes, of the same department.

College of Medical Evangelists, 1720 Brooklyn Ave. (33).

Addendum

During the preparation of this article we searched the medical literature for other descriptions of this syndrome and found only the Louis-Bar case of 1941. We have attempted to find out what since has happened to this case, but have not yet succeeded. We also corresponded with several of the leading authorities in the fields of neurology, cerebral palsy, and dermatology, and none had seen, heard, or read about such a syndrome.

In August, 1957, Frank R. Ford wrote that, since his earlier correspondence with us, he had seen a boy in his practice whom he believed might have this syndrome.[16] He also referred us to an article by Charles E. Wells and G. Milton Shy, of Bethesda, Md., published in May, 1957.[17] This beautifully illustrated article describes what is probably this same syndrome in two sisters, drawing attention to the familial nature of this syndrome, which the authors called progressive familial choreoathetosis with cutaneous telangiectasia. It is interesting that these girls, shown with hair styles covering their ears, have no telangiectasia of the ears.[18] We have written to the authors mentioning our cases and the Louis-Bar Case. They since have looked up this earlier reference and are convinced that this is all the same syndrome. On their request, we submit the apologies of Wells and Shy to Madame Louis-Bar for having overlooked her case report of 1941. Then in June, 1957, there was published the article, "Ataxia-Telangiectasia," by Elena Boder and Robert P. Sedgwick, of Los Angeles.[19] This interesting article gives a preliminary report on seven children (with an extra case history) including three sets of siblings and what appears to be the first autopsy report on this syndrome. It is noteworthy that these authors have such a large collection of cases of this rare condition. Drs. Boder and Sedgwick and we have become aware that we have a case in common (Case 7 of theirs and Case 1 of ours).‖ We have accounted for this in calculating incidence and statistics. In July, 1957, a report by A. Biemond, of Amsterdam, was read at the First International Congress of Neurological Sciences in Brussels. This paper, entitled "Palaeocerebellar Atrophy with Extrapyramidal Manifestations in Association with Bronchiectasis and Telangiectasis of the Conjunctiva Bulbi as a Familial Syndrome," presents four cases (including two autopsies) of apparently this same syndrome.[20]

Thus, there is the interesting situation in which prior to 1957 there was only 1 known case of this syndrome reported in the medical literature and within a three- to four-month period in 1957 there have been reported, published, or submitted for publication an additional 15 cases (including 4 autopsies) by four independent teams of investigators from three widely separated areas of the world. If one includes the unreported case of Frank R. Ford[16] and the three unreported cases of Douglas N. Buchanan[21] (these men have given us permission to mention their cases), the total of known cases to date is 20, involving 12 families and including 12 girls, 8 boys, and 7 pairs of siblings. There are approxi-

‖ Cyril B. Courville, who has studied both sets of slides from the autopsies of Case 1 of the Boder-Sedgwick series and Case 1 of ours, believes that they represent the same process.

mately an equal number of uninvolved siblings. It is interesting that nine of these cases are reported from Southern California. Thus, the evidence is good that this is an heredofamilial disorder, the transmission of which is probably by means of a simple autosomal recessive gene.

REFERENCES

1. Louis-Bar: Sur un Syndrome progressif comprenant des télangiectasies capillaires cutanées et conjonctivales symétriques, à disposition naevoïde et des troubles cérébelleux, Confinia neurol. 4:32-42, 1941.

2. Baron, D. N.; Dent, C. E.; Harris, H.; Hart, E. W., and Jepson, J. B.: Hereditary Pellegra-like Skin Rash with Temporary Cerebellar Ataxia, Constant Amino-Aciduria, and Other Bizarre Biochemical Features, Lancet 2:421-428, 1956.

3. Kaposi, M.: Idiopathisches, multiples Pigmentsarkom der Haut, Arch. Dermat. u. Syph. 4:265-273, 1872.

4. Bloom, D.: Congenital Telangiectatic Erythema Resembling Lupus Erythematosus in Dwarfs, A. M. A. Am. J. Dis. Child. 88:754-758, 1954.

5. Rendu, H.: Epistaxis répétées chez un sujet porteur de petits angiomes cutanés et muqueux, Bull. et mém. Soc. méd. hôp. Paris 13:731-733, 1896.

6. Osler, W.: On Multiple Hereditary Telangiectasis with Recurring Hemorrhages, Quart. J. Med. 1:53-58, 1907-1908.

7. Weber, F. P.: Multiple Hereditary Developmental Angiomata (Telangiectases of the Skin and Mucous Membranes Associated with Recurring Hemorrhages), Lancet 2:160-162, 1907.

8. von Hippel, E.: Über eine sehr seltene Erkrankung der Netzhant: Klinische Beobachtungen, von Graefes Arch. Ophth. 59:83-106, 1904.

9. Lindau, A.: Studien über Kleinhirncysten: Bau, Pathogenese und Beziehungen zur Angiomatosis retinae, Acta path. et microbiol. scandinav. (Supp.) 1:1-128, 1926.

10. Ford, F. R.: Diseases of the Nervous System in Infancy, Childhood and Adolescence, Ed. 3, Springfield, Ill., Charles C Thomas, Publisher, 1952.

11. Schut, J. W.: The Hereditary Ataxias, A. Res. Nerv. & Ment. Dis., Proc. 33:293-324, 1954.

12. van Bogaert, L.: Les Dysplasies neuro-ectodermiques congénitales, Rev. neurol. 63:353-398, 1935.

13. Yakovlev, P. I.: Congenital Ectodermoses (Neoplastic Malformation Affecting with Predilection the Skin, Retina, and Nervous System), in Blumer, G.: Practitioners Library of Medicine and Surgery, New York, D. Appleton-Century, 1936, Vol. 9, Chap. 27.

14. van der Hoeve, J.: Doyne Memorial Lecture: Eye Symptoms in Phakomatoses, Tr. Ophth. Soc. U. Kingdom 52:380-401, 1932.

15. Korbin, M. A.: Vertebral Angiography, A New Technique, read before the Western Neurosurgical Society, Pebble Beach, Calif., March, 1957.

16. Ford, F. R.: Personal communication to the authors.

17. Wells, C. E., and Shy, G. M.: Progressive Familial Choreoathetosis with Cutaneous Telangiectasia, J. Neurol., Neurosurg. & Psychiat. 20: 98-104, 1957.

18. Shy, G. M., and Wells, C. E.: Personal communication to the authors.

19. Boder, E., and Sedgwick, R.: Ataxia-Telangiectasia: A Familial Syndrome of Progressive Cerebellar Ataxia, Oculo-Cutaneous Telangiectasia, and Frequent Pulmonary Infection, Univ. Southern California M. Bull. 9:15-28, 1957.

20. Biemond, A.: Palaeocerebellar Atrophy with Extrapyramidal Manifestations in Association with Bronchiectasis and Telangiectasis of the Conjunctiva Bulbi as a Familial Syndrome, read before the First International Congress of Neurological Sciences, in Brussels, Belgium, July, 1957.

21. Buchanan, D. B.: Personal communication to the authors.

Promethazine Suppositories for Management of Nausea and Vomiting in Children

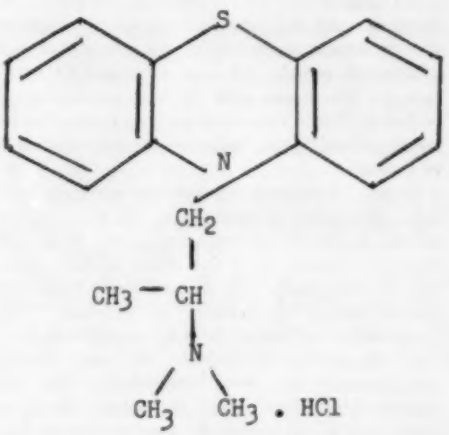
CAPT. THOMAS E. CONE JR. (MC), U.S.N.

Vomiting is a frequent and distressing complication of many illnesses common to childhood, and it is a particularly serious problem in infants. Loss of gastrointestinal fluids from severe and unrelieved emesis may cause dehydration and disturbance of electrolyte balance.[1]

The very nature of the disorder itself renders therapy difficult. Although sedation tends to discourage the inclination to vomit, the barbiturates have not proved especially effective for this purpose.[2] The vehicles—alcoholic suspensions and sweet syrups—used for many oral antinauseant agents may of themselves provoke or intensify emesis. The advantages of the rectal route are therefore obvious. A few trials of rectal medication with various antinauseant agents have been reported,[2-4] but no description of the management of vomiting with promethazine (Phenergan, Wyeth Laboratories, Inc.) in suppository form has thus far appeared.

Promethazine (10-[2-dimethylaminopropyl] phenothiazine hydrochloride) is primarily an antihistamine (Figure) which was introduced for treatment of all types of allergic disorders more than eight years ago. The diversity of pharmacological properties possessed by this compound, including definite sedative and antiemetic activities, was soon realized. Early clinical trials of the antinauseant action concerned the control of vomiting in pregnancy,[5,6] irradiation,[7] and motion sickness.[8,9] Additional studies[10-18] established the antinauseant activity of promethazine for the nausea and vomiting that renders air, sea, and other types of travel an ordeal for many persons. The compound was first used to control postanesthetic vomiting in 1952.[19] This report was followed by numerous others.[20-25]

Promethazine Hydrochloride



The exact site of the activity exerted by the various antiemetic agents is not known. Chinn and Smith[26] have suggested that an antagonistic action on acetylcholine or related substances in the central nervous system may play a major role. These investigators believe that, in view of the findings in earlier pharmacological studies, the primary areas must be subcortical, since (*a*) motion sickness can be produced in completely decerebrate dogs, (*b*) little prophylactic effect is obtainable from strong central nervous system depressants unless such agents are administered in large doses, (*c*) some active antinauseants have little or no

Received for publication Aug. 5, 1957; accepted Sept. 26.

Pediatrics Service, U. S. Naval Hospital, Bethesda, Md.

The opinions or assertions contained herein are the private ones of the writer, and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

central depressant action, and (*d*) the central nervous system depression produced by others may be counteracted by an analeptic without destroying the antiemetic effect. Although the site of action exerted by promethazine has not been established, it is believed that the compound acts mainly on the subcortical regions.

Method

Promethazine was administered in the form of rectal suppositories to 150 children for control of vomiting. All the patients were under treatment on our service in the clinics and wards during a nine-month period. All were examined by members of the house staff in the department of pediatrics. Blood cell counts were performed before treatment was begun, and stool cultures were taken as indicated.

Group 1 comprised 100 children suffering from acute nonspecific gastroenteritis. In this disorder emesis is usually of explosive onset; frequently there is a history of similar illness in other members of the family. On physical examination the patient shows no evidence of infection. The temperature is normal or only slightly elevated. The disease is self-limited; the only serious complications are acute dehydration, with the accompanying fever, and electrolyte imbalance consequent to the persistent vomiting. Early control of vomiting is essential, to permit oral administration of a hypotonic polyionic electrolyte solution, as described by Darrow.[27]

In the patients in this series the blood cell count was nonspecific; no pathogens were demonstrated in cultures of the stool. Vomiting was followed by diarrhea in 24 to 48 hours.

Group 2 included 20 children in whom vomiting was a prominent symptom of infectious process, as streptococcal pharyngitis, otitis media, pyelonephritis, or cystitis (parenteral vomiting).

Group 3 comprised 20 children who were susceptible to motion sickness, especially during automobile trips.

Group 4 included 10 children, 6 of whom were undergoing deep abdominal irradiation for neuroblastoma and retroperitoneal sarcoma and 4 of whom were receiving mechlorethamine (nitrogen mustard) therapy.

Dosage.—Suppositories containing 12.5 mg. of promethazine were administered to children less than 5 years of age; for older children, 25 mg. suppositories were used.

The suppository was inserted digitally beyond the sphincter, and the buttocks were held firmly together for five minutes to prevent expulsion. For outpatients the physician demonstrated to the parents the proper method of administration. The progress of outpatients was determined by reexamination in the clinics and from telephoned reports from the homes.

Group 1: All food was discontinued, and an electrolyte solution (Lytren, Mead Johnson & Company,) was administered orally as required. A promethazine suppository was inserted at the time of the initial examination, and was repeated in six hours. In a few cases a third suppository was used in an additional six hours. The electrolyte solution was continued by mouth after the vomiting was checked. Boiled skim milk was fed during the diarrheal period.

Group 2: Promethazine suppositories were administered as for Group 1, in association with appropriate antibiotic and antipyretic measures.

Group 3: A promethazine suppository was inserted one hour before the start of a trip and repeated every six hours as necessary.

Group 4: A promethazine suppository of 25 mg. was administered on the morning of each scheduled roentgen treatment throughout the prescribed course. For the four patients under treatment with mechlorethamine, a promethazine suppository was inserted approximately one hour before the intravenous administration of the substance.

Evaluation of Results: Results were evaluated as (*a*) good if there was no further emesis after administration of 1 promethazine suppository and (*b*) fair if one to four episodes occurred after administration of the suppository. The treatment was considered a failure if the patient vomited more than four times after administration of 1 suppository.

Results

Control of vomiting was good to fair in 90% (Table). Promethazine suppositories were of extreme value and represent a real advance in the treatment of nausea and vomiting in acute nonspecific gastroenteritis. On prompt control of the emesis the oral nutritive solution was retained; hence serious complications were prevented.

One suppository sufficed to control vomiting in 77% (good result), and for 13%, with fair result, a second suppository, and in a few cases a third, was required. Ten per cent were not relieved.

Emesis was controlled by 1 suppository in the four patients undergoing mechlorethamine therapy and in five of the six

Results of Use of Promethazine Suppositories for Control of Vomiting Associated with or Resulting from Various Conditions in 150 Children

	Results, No.			
	Good	Fair	Poor	Total
Acute nonspecific gastroenteritis	75	14	11	100
Infectious processes	14	3	3	20
Motion sickness	18	2	0	20
Irradiation	5	1	0	6
Mechlorethamine therapy	4	0	0	4
Per cent of total cases	77	13	10	

receiving deep irradiation of abdominal malignant tumors. The sixth patient experienced a fair result. Since these patients experienced only slight nausea, their appetites remained good.

The quiescent effect produced by promethazine was, of course, an advantage for all, especially the children suffering from infection and those subject to motion sickness. The attendants charged with the management of these children remarked on their greater tractability.

Almost all the children slept four to six hours after insertion of each suppository. However, none showed any evidence of lethargy or depression of the sensorium. All could be aroused easily for nursing attentions.

There were no toxic effects and no clinical signs of rectal irritation. None of the patients complained of discomfort after insertion of the suppository.

Summary and Conclusions

A single promethazine suppository effectively controlled vomiting in 77% of the 150 children for whom it was prescribed.

Promethazine suppositories were as effective in the treatment of vomiting of nonspecific gastroenteritis (75 of 100 children treated) as in the control of parenteral vomiting in a smaller number of children.

Suppositories containing 12.5 mg. of promethazine were administered to children less than 5 years of age; for older children, 25 mg. suppositories were used.

Department of Pediatrics, National Naval Medical Center, Bethesda 14, Md.

REFERENCES

1. Nelson, W. E.: Digestive Disturbances, in Textbook of Pediatrics, Ed. 6, Philadelphia, W. B. Saunders Company, 1954, p. 666.

2. Daeschner, C. W.; Clark, J. L.; George, G. Y., and Frankel, R. A.: Chlorpromazine in the Control of Vomiting in Children: Preliminary Clinical Evaluation, A. M. A. Am. J. Dis. Child. 89:525-530, 1955.

3. Beaumont, F. K.: Antihistamine Drugs and Seasickness, Correspondence, Brit. M. J. 2:1472-1473, 1949.

4. Daeschner, C. W.; Colgan, M.; Brewer, E.; Foster, J., and Bashaw, C.: An Evaluation of Antiemetic Agents in the Control of Vomiting in Children, South. M. J. 49:1465-1469, 1956.

5. Dougray, T.: Antihistamines in the Treatment of Nausea and Vomiting of Pregnancy, Brit. M. J. 2:1081-1083, 1949.

6. Black, J. R.: Antihistamines in Pregnancy, M. J. Australia 1:853-854, 1950.

7. Salva, J. A., and Badell, M.: Treatment of Radiation Sickness with a Synthetic Antihistamine, Presse méd. 63:888, 1949.

8. Ambrus, J. L., and Ambrus, C. M.: Motion-Sickness and Anti-Histamines, Lancet 1:326, 1950.

9. Harper, J.: Prevention and Treatment of Travel Sickness with Promethazine Chlorotheophyllinate, Lancet 1:1141, 1951.

10. MacKay, R. A., and Ferguson, J. K. W.: Influence of Certain Anti-Motion-Sickness Drugs on Psychomotor and Mental Performance, J. Aviation Med. 22:194-195, 1951.

11. Chinn, H. I.; Handford, S. W.; Cone, T. E., Jr., and Smith, P. K.: The Effectiveness of Various Drugs for the Prophylaxis of Seasickness, Am. J. Med. 12:433-439, 1952.

12. Chinn, H. I., and Milch, L. J.: Comparison of Airsickness Preventives, J. Appl. Physiol. 5: 162-164, 1952.

13. Chinn, H. I.; Gammon, W. R., and Frantz, M. E.: Prevention of Airsickness Among Airborne Troops, J. Appl. Physiol. 5:599-602, 1953.

14. Chinn, H. I., et al.: Evaluation of Some Drugs in Seasickness, J. Pharmacol. & Exper. Therap. 108:69-79, 1953.

15. Remedies for Seasickness, Lancet 2:437-438, 1953.

16. Chinn, H. I.; Strickland, B. A., Jr.; Waltrip, O. H., and McGeary, J. D.: Prevention of Airsickness During Training Flights, U. S. Armed Forces M. J. 4:1609-1612, 1953.

17. Handford, S. W.; Cone, T. E., Jr.; Chinn, H. I., and Smith, P. K.: Drugs Preventing Motion Sickness at Sea, J. Pharmacol. & Exper. Therap. 111:447-453, 1954.

18. Conner, P. K., Jr., and Moyer, J. H.: A Therapeutic Appraisal of Antiemetic Agents, GP 14:125-139, 1956.

19. Holzman, L., and Josipowicz, A.: Clinical Evaluation of Promethazine for Pre- and Postanesthetic Sedation, Am. Pract. & Digest Treat. 7:939-942, 1956.

20. Carroll, J. J., and Hudson, P. W.: Chlorpromazine and Promethazine in Obstetrics, Canad. Anaesthesiol. Soc. J. 2:340-346, 1955.

21. Dillon, G. P.: Clinical Evaluation of Promethazine for Prevention of Postoperative Vomiting, Am. Pract. & Digest Treat., to be published.

22. Light, G. A.; Morch, E. T., and Cunningham, J. J.: Promethazine (Phenergan) as an Adjunct to Anesthesia: Preliminary Clinical and Animal Studies, J. A. M. A., to be published.

23. Wohlgemuth, P. R., and O'Brien, G. R.: Postoperative Edema in Maxillofacial Surgery, Prevention and Treatment with Promethazine, Am. J. Surg., to be published.

24. Sadove, M. S.: Promethazine in Surgery, J. A. M. A. 162:712-715, 1956.

25. Sadove, M. S., and Frye, T. J.: Preoperative Sedation and Production of a Quiescent State in Children, J. A. M. A., to be published.

26. Chinn, H. I., and Smith, P. K.: Motion Sickness, Pharmacol. Rev. 7:33-82, 1955.

27. Darrow, D. C.: Therapeutic Measures Promoting Recovery from Physiologic Disturbances of Infantile Diarrhea, Pediatrics 9:519-533, 1952.

The Urinary Excretion of Porter-Silber Chromogens by Premature Infants

ROBERT L. CRANNY, M.D., and CAROLINE L. CRANNY, M.T., Salt Lake City

The over-all pattern of the physiologic and biochemical functions of the normal human adrenal cortex of older children and adults has been the subject of considerable study. Much less is known concerning the functional pattern of this gland in premature and full-term infants. Venning et al.,[1] using a bioassay method, found no differences in the urinary excretion of glucocorticoids in premature and full-term infants during the first 10 days of life. Unfortunately, in their study "several" samples were "pooled," and since no information is given concerning the selection of samples for pooling it is not possible to interpret their data with assurance. It is noteworthy that these authors found no measurable glucocorticoids in the extracts of three normal homogenized human placentas.

Di George et al.[2] have reported a very high plasma level of neutral 17-ketosteroids in an anencephalic infant who was studied during the period of 25 hours that he lived. Inasmuch as almost no adrenal cortex could be found on histologic examination of the patient's adrenal glands (the total weight of the two glands in this patient was 0.75 gm., as compared with the average normal of 6 gm.) the authors' proposal of the placental or maternal origin of the compounds in question seems the most likely explanation in this patient.

Recently, Lanman[3] found no significant increase with age in the urinary excretion of formaldehydogenic steroids in premature infants during the first 10 days of life but a highly significant increase ($P=0.001$) if the patients were studied over a longer period of time. It is the purpose of the present communication to report the results of a study of the urinary excretion of 17-hydroxycorticosteroids of premature infants.

Materials and Methods

A total of 63 twenty-four-hour urine specimens were collected from 21 surviving patients (11 boys and 10 girls). Three samples were collected from each patient. The first sample was collected during the first three days of life; the second sample, between Day 4 and Day 14, and the third sample, between Day 15 and Day 40. To facilitate the collection of specimens, a hole, 3 in. in diameter, was cut entirely through a crib mattress. The mattress was covered with a plastic or a rubber sheet, and a stainless steel receptacle of appropriate size was fitted snugly into the defect. The infant was then loosely restrained in a prone position in such a way that the genitalia were positioned over the receptacle. The urine was collected as voided and was immediately placed in a refrigerator. After each specimen was completed, it was stored in a frozen state until analyzed. Since, in our laboratory, deliberate gross fecal contamination of several samples of urine obtained from healthy children had no detectable effect on the determination of urinary Porter-Silber chromogens, no effort was made to avoid fecal contamination during collection. Feces was removed by filter-paper filtration. Only patients who had had an "uneventful course" were included in this study. The birth weights ranged from 1390 to 2420 gm. It was determined statistically that there was no bias in the

Submitted for publication Nov. 15, 1957.

This work was supported by a grant-in-aid from Mead Johnson & Company, Evansville, Ind.

Presented in part at the meeting of The Western Society for Pediatric Research, Salt Lake City, Oct. 23, 1956.

Assistant Professor of Pediatrics (Dr. Cranny), Department of Pediatrics, The University of Oklahoma School of Medicine, Oklahoma City. Present address: Department of Pediatrics, the University of Utah College of Medicine. University of Utah College of Medicine Department of Pediatrics, Salt Lake City (C. L. Cranny).

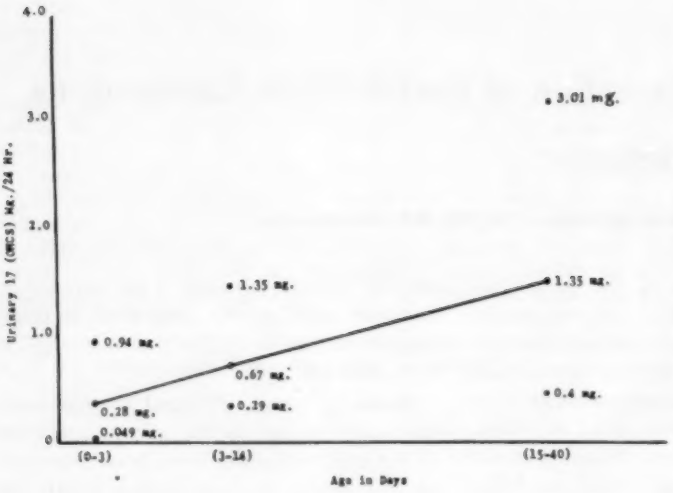


Fig. 1.—Average excretion of 17-hydroxycorticosteroids during the first 40 days of life. The line connects the average of the values obtained for the group of 21 patients during the intervals shown. The highest value and the lowest value obtained in the group at the designated ages are represented by the data above and below the line, respectively.

selection of cases (no predominance of heavier over lighter infants or vice versa).

The urinary Porter-Silber chromogens were determined by a modification of the Reddy-Jenkins-Thorn technique.[4,5] For the purpose of this report these chromogens will be considered to be 17-hydroxycorticosteroids. Purification of the butyl alcohol by redistillation proved to be a critical point in reducing the chromogens that are present in the purest grades of commercially available butyl alcohol.

Urine blanks, standards at various dilutions, and reagent blanks were run with each set of determinations. Cortisone (17-hydroxy-11-dehydrocorticosterone) in butyl alcohol was used as the standard.* When enough urine was available, duplicate determinations were done.

Results

The data are expressed as linear functions of birth weight and age, of body weight at the time of excretion and age, and of each of these variables separately.†

Average Values.—As demonstrated in Figure 1, the average value for the 24-hour urinary excretion of 17-hydroxycorticosteroids during the first three days of life was 0.28 mg., with a minimum of 0.049 mg. and a maximum of 0.94 mg. Between the 4th and the 14th days of age the average excretion was 0.67 mg., with a minimum of 0.29 mg. and a maximum of 1.35 mg. Between the 15th and the 40th days of age the average excretion was 1.35 mg., with a minimum of 0.40 mg. and a maximum of 3.01 mg. It will be noted that the highest single excretion, 3.01 mg., is barely within the lower range of normal that is usually given for adults. It is also of interest that the average of the sum of the highest individual excretions of each of the patients (1.42 mg. per 24 hours) is considerably below that of normal adult levels (Table 1).

Correlation of Excretion with Age and Birth Weight.—When age and birth weight were considered simultaneously they were found to correlate with the urinary excretion of 17-hydroxycorticosteroids at the 0.1% level with a coefficient of multiple correlation of 0.813.

TABLE 1.—*Comparison of the Average of the Sum of the Single Highest Twenty-Four-Hour Urinary Excretion of 17-Hydroxycorticosteroids of Each Premature Infant Studied with the Range of Excretion of Normal Adults in Our Laboratory*

	17-OHCS Excretion, Mg./24 Hr.
Av. of the highest excretions of all patients	1.42
Range of normal adults in our laboratory	2.5-8.0

*Furnished by Dr. Charles D. Kochakian.

†The staff of the division of vital statistics, Oklahoma State Department of Health, aided in the statistical evaluation of the data.

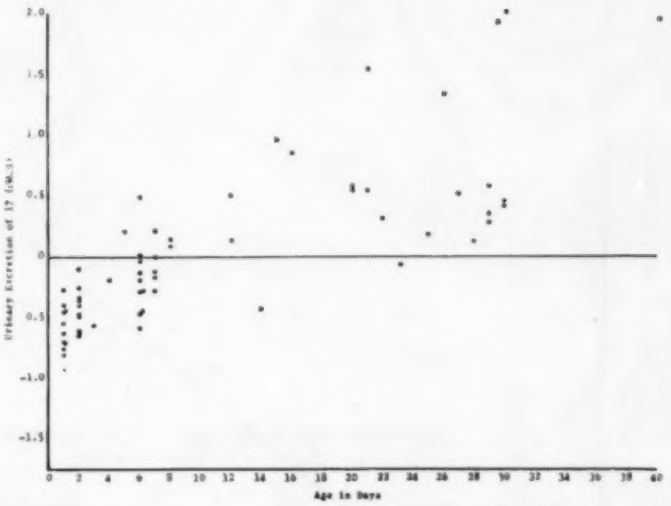


Fig. 2.—Regression equation correlation of excretion of 17-hydroxycorticosteroids with age; birth weight statistically controlled. Partial coefficient of correlation $R = 0.798$; $P = 0.001$. Highly significant.

In an attempt to evaluate the individual components of this three-dimensional graph, the two variables of the equation were evaluated.

Correlation of Excretion with Age; Birth Weight Statistically Controlled: When birth weight was statistically controlled so that it exerted a constant influence on the equation (Fig. 2), the partial coefficient of correlation of the urinary excretion of 17-hydroxycorticosteroids and age was 0.798, with a P value of 0.001.

Correlation of Excretion with Birth Weight; Age Statistically Controlled: When age was statistically controlled (Fig. 3) so that it exerted a constant influence on the equation, the partial coefficient of correlation of the urinary excretion of 17-hy-

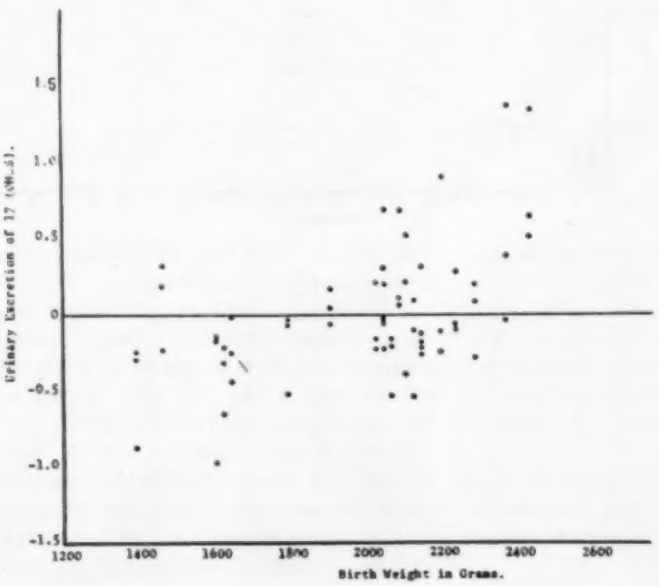


Fig. 3.—Regression equation correlation of excretion of 17-hydroxycorticosteroids with birth weight; age statistically controlled. Partial coefficient of correlation $R = 0.497$; $P = 0.001$. Highly significant.

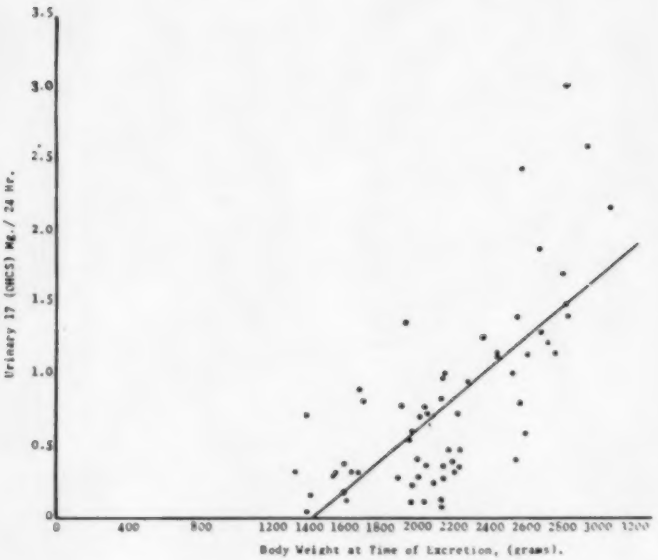


Fig. 4.—Linear correlation of excretion with body weight at the time of excretion. Coefficient of linear correlation $R=0.712$; $P=0.001$. Highly significant.

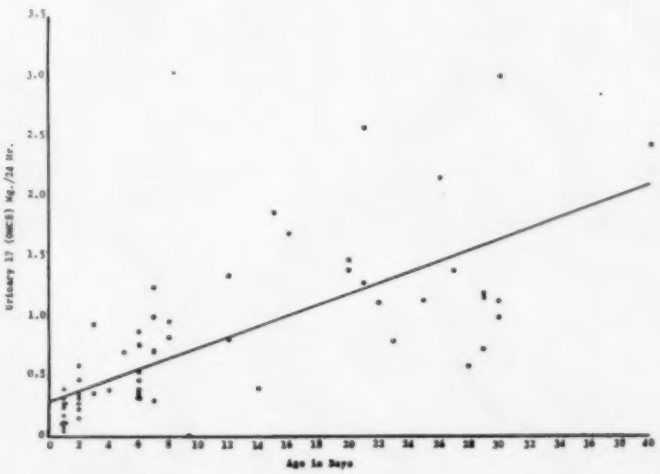


Fig. 5.—Linear correlation of excretion with age. Coefficient of linear correlation $R=0.741$; $P=0.001$. Highly significant.

droxycorticosteroids and birth weight was 0.497, with a P value of 0.001.

Correlation of Excretion with Body Weight at the Time of Excretion.—The coefficient of linear correlation between excretion and body weight at the time of excretion was 0.712, with a P value of 0.001 (Fig. 4).

Linear Correlation of Excretion with Age.—The linear correlation between excretion and age (Fig. 5) was 0.741, with a P value of 0.001.

It will be noted that all of these correlations are highly significant.

Relationship Between Excretion and Birth Weight.—The relationship between excretion and birth weight (Fig. 6) is significant only at the 5% level, with a coefficient of linear correlation of 0.256.

Birth Weight Compared with Body Weight as a Standard.—The difference between the correlation coefficient of excretion to age and birth weight ($r=0.813$) and the correlation coefficient of excretion

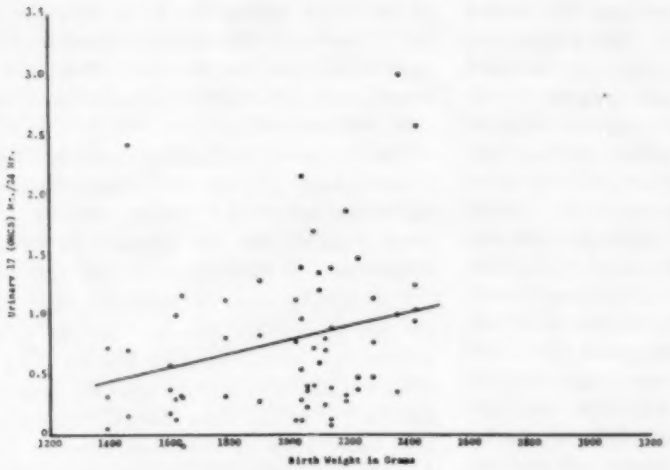


Fig. 6.—Linear correlation of excretion with birth weight. Coefficient of linear correlation $R=0.256$; $P=0.05$. Not significant.

to age and body weight at the time of excretion ($r=0.786$) is not statistically significant. This indicates that either of these data will serve as a satisfactory guide to expected excretion.

Urine Volume and Total Excretion.—The urine volumes of the patients studied increased with chronologic age (Table 2). The correlation between the urine volume and the total excretion of 17-hydroxycorticosteroids per 24 hours was significant at the 1% level, with a coefficient of 0.698. An inverse correlation, which was significant at the 2% level, existed between the urine volume and the excretion per cubic centimeter of urine.

Comment

There is much confusion over the interpretation of the results of urinary 17-hydroxycorticosteriod determinations. These compounds are excreted in the urine in both the free and the conjugated forms. The conjugates are mostly glucuronides. The results obtained from a given specimen will depend on several factors: the temperature of storage, whether or not the specimen was subjected to hydrolysis prior to extrac-

TABLE 2.—*Relation of 17-Hydroxycorticosteroid Excretion and Urine Volume*

Patient	Sex	Age 1–3 Days		Age 4–14 Days		Age 15–40 Days	
		Urine Volume	17-OHCS, Mg./24 Hr.	Urine Volume	17-OHCS, Mg./24 Hr.	Urine Volume	17-OHCS, Mg./24 Hr.
1	M	22	0.126	75	0.290	150	0.906
2	F	17	0.243	180	0.704	210	0.797
3	M	92	0.116	145	0.778	280	1.129
4	F	93	0.474	60	0.709	300	1.139
5	M	12	0.179	60	0.379	230	0.582
6	F	49	0.279	135	0.827	230	1.288
7 *	M	96	0.598	170	1.358	320	1.21
8 *	F	47	0.319	165	0.807	325	1.131
9	M	22	0.282	225	0.968	240	1.40
10	M	120	0.350	145	1.0	185	3.01
11	M	14	0.126	205	0.389	250	0.815
12	M	80	0.366	120	0.470	240	1.48
13	M	66	0.116	155	0.539	275	2.16
14	F	52	0.322	66	0.313	260	1.167
15	M	25	0.227	135	0.358	115	0.40
16	F	155	0.274	170	0.322	245	1.87
17 *	F	60	0.075	175	0.886	200	1.302
18 *	F	22	0.049	170	0.322	115	0.727
19	F	50	0.940	325	1.253	340	2.58
20	F	33	0.130	80	0.710	195	2.43
21	M	31	0.406	250	0.720	292	1.70
Mean±E. M.		69.1±5.9 56±8.4	0.28±0.044	146.6±14.7	0.67±0.066	236.5±13.78	1.35±0.146

* Twins.

tion, the choice of solvent, and the method and extent of extraction. The temperature at which the specimen is collected and stored may influence the results because of the possibility that hydrolysis may occur if the specimen is kept at other than freezing temperatures. The solvent used for extraction will have a direct bearing on the results obtained because of the selective solubilities of the compounds in question, i. e., both free and conjugated 17-hydroxycorticosteroids will be extracted by butyl alcohol, whereas only the nonconjugated forms will be extracted by other commonly used solvents, such as chloroform. The type and duration of hydrolysis will influence the results quantitatively. Although both acid and β-glucuronidase hydrolyze the glucuronide conjugates, β-glucuronidase is more efficient. Repeated incubation with this enzyme will further increase the yield of measurable steroid. If the urine sample is subjected to neither acid nor enzyme (β-glucuronidase) hydrolysis, the yield of measurable 17-hydroxycorticosteroid will represent the free steroids only, unless butyl alcohol is the solvent used.

Chronologic excretion was not related in a statistically significant fashion to birth weight unless the factor of age was considered simultaneously. The finding of a highly significant relationship between excretion and age may indicate that the physiologic function of the adrenal cortex in premature infants changes as the infant becomes older. Further support for this concept may be found in the lack of a statistically significant relationship between excretion and birth weight, whereas a highly significant relationship exists between excretion and body weight at the time of excretion.

It is apparent from the data (Table 2) that the urinary excretion of 17-hydroxycorticosteroids in these patients increased as the patients became older. It is tempting to postulate that the activity of the adrenal cortex increases as the premature infant becomes older. However, the high degree of correlation between the urine volume and the 17-hydroxycorticosteroid excretion indicates that the excretion of these compounds may be influenced by increases in urine volume.

The inverse relationship between the urine volume and the 17-hydroxycorticosteroid excretion per cubic milliliter of urine suggests that the influence of urine volume may be more apparent than real.

The daily volume of urine excreted by the newborn infant increases for the first several days of extrauterine life but thereafter remains relatively constant for several months.[6,7] It has been shown repeatedly that many tests of the renal function of full-term neonatal infants indicate an efficiency of only 20% to 60% of that of adults when they are compared on a unit surface area basis.[8,9,10] Only incomplete data on the renal function of premature infants are available, but it has been shown by Gordon et al.[11] that the urea clearance of premature infants is significantly less than the urea clearance of full-term infants at comparable postpartum ages. These investigators found no relationship between urea clearances and urine flow—even when the urine flow was augmented by from 25% to 50%. This is at variance with the results of McCance et al.[12] and Young et al.,[13] who found that up to a certain point (urine volume greater than 2 cc. per minute) urea clearance was increased by increases in minute volume. However, they also found that at similar minute volumes the urea clearances of premature infants were much less than those of full-term infants.[13] At present it is not known whether significant changes in renal function occur during the first month of life in premature infants. Although our data indicate that a change in 17-hydroxycorticosteroid metabolite excretion occurs during the first month of life in premature infants, it is not known whether this change is independent of renal function.

It has been stated, by at least one author,[14] that urinary corticoid excretion is

affected by urinary clearance rates. While this is possible, it remains unproved. Both blood and urine 17-ketosteroids are normally elevated at birth and gradually decrease over the first two weeks in full-term infants and over the first two to four weeks in premature infants. Since renal function increases in efficiency during this time in full-term infants, the decreasing 17-ketosteroid excretion pattern would seem to be evidence against renal function as an important factor in the pattern of urinary steroid excretion at these ages. If a direct relationship existed between renal function and 17-ketosteroid excretion, one would logically expect an increasing rather than a decreasing 17-ketosteroid excretion pattern. Whether this would hold true is a matter for speculation, since 17-ketosteroid production decreases during the neonatal period and normally remains low for several years thereafter. Correlated data on blood levels of the 17-hydroxycorticosteroids during the periods studied and the use of radioactive steroids to determine blood disappearance rates and the subsequent urinary recovery of the tagged steroid metabolites would allow for a more complete interpretation of the present data.

The lack of relationship between the urinary excretion of 17-hydroxycorticosteroids and 17-ketosteroids might be interpreted to mean that the 17-ketosteroids are synthesized by a portion of the infant adrenal cortex whose function declines after birth. Although the possibility of an anatomic difference causing the dissociation between the urinary excretion of 17-ketosteroids and 17-hydroxycorticosteroids remains unproved, there is much indirect evidence to support this concept. It has been demonstrated repeatedly that prior to 20 weeks of gestation the adrenal cortex of anencephalic monsters is histologically similar to that of a normal conceptus of the same gestational age but that thereafter the fetal zone atrophies to the point of disappearance in the former.[15] Similar fetal zone involution has been demonstrated by Benirschke et al.[15] in children with hydrocephaly, hemianencephaly, and cephalomeningocele, provided there was destruction of or reduction in the size of the hypothalamus. This is consistent with the mechanism of fetal adrenal cortex stimulation as proposed by these authors and others, as follows: Under normal circumstances it is possible that during the first half of pregnancy the fetal adrenal cortex is maintained by the luteinizing properties of the chorionic gonadatropin and during the last half of pregnancy the high concentration of maternal estrogens stimulates the hypothalamus, which, by a neurosecretory mechanism, in turn stimulates the anterior pituitary to produce luteinizing hormone. The fetal zone is thus maintained until delivery. Inasmuch as C_{19} steroids have been found in the extracts of the adrenal glands of fetuses between 9½ and 21 weeks of gestation[16] and 17-α-hydroxycorticosterone was found in trace amounts in the same fetuses after 16 weeks of gestation, one must consider the possibility of a postpartum alteration in the activity of the enzyme systems involved in steroidogenesis. It is also possible that the 17-ketosteroids are extrafetal in origin.[2]

The function of the adrenal cortex is believed by some to be closely related to body surface area.[3,17] If this is true, the differences between the urinary adrenal metabolite excretion of adults or older children and that of premature infants are relative. Ulstrom's[18] finding of a qualitative as well as a quantitative difference in the urinary excretion of androgens by the premature infant when compared with the full-term infant and our finding of an inverse relationship between the urine volume and the excretion of 17-hydroxycorticosteroids per cubic centimeter of urine do not support this thesis.

The lack of correlation between body weight and body length in premature infants is well known. A great variation in the body weights of premature infants of a given length occurs. Inasmuch as in-

creases in the body weights of the smaller premature infants are usually minimal during the first two weeks of life, the body surface area changes must be minute. Although it has been shown that a direct relationship exists between the logarithms of body weight and body surface area (as measured directly) in prenatal life,[19] it is possible that this relationship does not hold for newborn infants during the first week of life, when they are experiencing a weight loss. If this is true, it logically follows that the calculation, during the first week of life, of body surface areas by any method which utilizes body weight may result in erroneous surface area values. Whether the error would be large enough to influence the interpretation of a given set of data poses a serious question.

Regardless of correlations with various baselines, such as age or, as proposed by some investigators, body surface area, the values that are reported from the laboratory are the data with which the clinician must work. It is important that the clinician be aware of the differences between the normal values for various age groups and that he have an appreciation of the influences that differences in method of determination can have on the final results, so that his interpretation of the laboratory data will be correct.

Since the average 24-hour urinary excretion of 17-hydroxycorticosteroids in the patients studied was less than that of normal adults, it would appear that appropriately smaller normal values must be applied when referring to premature infants. Further study will be necessary to establish whether the adrenal cortical function of premature infants is less than that of other patients.

Summary

The urinary excretion of 17-hydroxycorticosteroids by the premature infant increases during the first 40 days of extrauterine life. The correlation between excretion and chronologic age is statistically highly significant.

The urinary excretion of 17-hydroxycorticosteroids is not significantly correlated with birth weight unless the factor of age is considered simultaneously.

The relationship between the urinary excretion of 17-hydroxycorticosteroids and body surface area may not be a consistent one.

The influence of renal function, as such, on the urinary excretion of adrenocortical metabolites by the premature infant is not yet clearly defined.

Helen August, R.N., and the nursing staff of the premature nursery of the University of Oklahoma Hospitals assisted in this study.

Department of Pediatrics, University of Utah College of Medicine.

REFERENCES

1. Venning, E. H.; Randall, J. P., and György, P.: Excretion of Glucocorticoids in the Newborn, Endocrinology 45:430, 1949.

2. Di George, A. M.; Arey, J. B., and Bongiovanni, A. M.: Plasma 17-Ketosteroids in an Anencephalic Infant, J. Clin. Endocrinol. 16:1281, 1956.

3. Lanman, J. T.: Function of Adrenal Cortex in Premature Infants, Pediatrics 11:120, 1953.

4. Reddy, W. J.; Jenkins, D., and Thorn, G. W.: Estimation of 17-Hydroxycorticosteroids in Urine, Metabolism 1:511, 1952.

5. Reddy, W. J.: Modification of the Reddy-Jenkins-Thorn Method for the Estimation of 17-Hydroxycorticosteroids in Urine, Metabolism 3:489, 1954.

6. Thomson, J.: Observations on the Urine of the Newborn Infant, Arch. Dis. Childhood 19:169, 1944.

7. Cranny, R. L.: Unpublished data.

8. Barnett, H. L., and Comell, J. V.: The Physiologic and Clinical Significance of Immaturity of Kidney Function in Young Infants, J. Pediat. 42:99, 1953.

9. Barnett, H. L.; Hare, W. K.; McNamara, H., and Hare, R. S.: Influence of Post Natal Age on Kidney Function of Premature Infants, Proc. Soc. Exper. Biol. & Med. 69:55, 1948.

10. Barnett, H. L.; Hare, K.; McNamara, H., and Hare, R.: Measurement of Glomeruli Filtration Rate in Premature Infants, J. Clin. Invest. 27:691, 1948.

11. Gordon, H. H.; Harrison, H. E., and McNamara, H.: The Urea Clearance of Young Premature and Full Term Infants, J. Clin. Invest. 21:499, 1942.

12. McCance, R. A., and Young, W. F.: The Secretion of Urine by Newborn Infants, J. Physiol. 99:265, 1941.

13. Young, W. F.; Hallum, J. L. and McCance, R. A.: The Secretion of Urine by Premature Infants, Arch. Dis. Childhood 16:243, 1941.

14. Klein, R.; Fortunato, J., and Papadatos, C.: Free Blood Corticoids in the Newborn Infant, J. Clin. Invest. 33:35, 1954.

15. Benirschke, K.; Bloch, E., and Hertig, A. T.: Concerning the Function of the Fetal Zone of the Human Adrenal Gland, Endocrinology 58:598, 1956.

16. Bloch, E.; Benirschke, K., and Rosemberg, E.: C_{19} Steroids, 17α-Hydroxycorticosterone and a Sodium Retaining Factor in Human Fetal Adrenal Glands, Endocrinology 58:626, 1956.

17. Read, C. H.; Venning, E. H., and Ripstein, M. P.: Adrenal Cortical Function in Newly Born Infants, J. Clin. Endocrinol. 10:845, 1950.

18. Ulstrom, R. A., and Doeden, D.: Chromatographic Studies of Urinary Steroids in Term and Premature Infants, in Adrenal Function in Infants and Children—A Symposium, edited by L. I. Gardner, New York, Grune & Stratton, Inc., 1956, p. 31.

19. Klein, A. D., and Scammon, R. E.: Relations Between Surface Area Weight and Length of the Human Body in Prenatal Life, Proc. Soc. Exper. Biol. & Med. 27:456, 1930.

IF YOU CHANGE ADDRESS

Please notify us at least six weeks before you make the change.

With your notification, include the address label clipped from the latest copy of the journal. If your city has postal zone numbers, be sure to include the zone number in your new address.

You will want to get your copies promptly; so notify us at least six weeks in advance. Send your change notice to

A. M. A. Journal of Diseases of Children

American Medical Association
535 North Dearborn St.
Chicago 10, Illinois

Case Reports

Female Pseudohermaphroditism with Penile Urethra

Report of an Unusual Case of Congenital Adrenal Hyperplasia

LORIN E. AINGER, M.D.; GERARDO C. ZAPATA, M.D.; ROBERT S. ELY, M.D., and VINCENT C. KELLEY, M.D., Ph.D., Salt Lake City

The extent to which masculinization of the external genitalia occurs in the female pseudohermaphrodite with congenital adrenal hyperplasia is variable. The usual patient with this condition shows some clitoral enlargement with chordee, a urethra and vagina opening into a urogenital sinus which has its external aperture at the base of the clitoris, and some degree of corrugation and fusion of the labia majora simulating a scrotum. Several cases with the urethra coursing partially or entirely through the phallus have been reported. The most extreme degree of masculinization is represented by the development of the phallus into a penile structure with the urethra pursuing a normal course and opening at the tip of the glans and with fusion of the labia to resemble a scrotal structure. Patients with this configuration of the external genitalia resemble cryptorchid males with macrogenitosomia praecox due to congenital adrenal hyperplasia. Only three such cases previously have been reported,[1-3] and none was diagnosed before necropsy. The case to be reported here probably represents the first such case to be diagnosed correctly during life.

Report of a Case

History.—The patient was admitted to the Salt Lake General Hospital on April 25, 1955, at the age of 3 years for evaluation and treatment of advanced sexual and somatic development. The provisional diagnosis by the referring physician was macrogenitosomia praecox due to congenital adrenal hyperplasia. The patient had a birth weight of 6 lb. 14 oz. and was born by spontaneous vertex delivery following a full-term uneventful pregnancy. At birth the child appeared to be a normal boy, although the grandmother had commented that "the genitalia were somewhat larger than those of other babies." Growth during the first year of life was somewhat slow, the weight at one year of age being 19 lb. The child was noted to have salt-craving at about 1 year of age, to have pubic hair and an increasing size of the penis at approximately 18 months of age, and to have definite growth acceleration at 2 years of age.

Past History.—There was no history of adrenocortical crises. The patient had enjoyed comparatively good health prior to this hospitalization, having had only rubella and chickenpox without complications and one febrile convulsion associated with an upper respiratory infection.

Family History.—There were two siblings. A 5-year-old sister was apparently normal. A one-year-old sister was admitted to this hospital at the same time for sex determination. This child was found to have typical female pseudohermaphroditism with congenital adrenal hyperplasia.

A cousin of the patient had "glandular trouble" referable to the adrenal glands and a "big head." A cousin of the patient's father was said to be effeminate and to have "something wrong with the genitals." A maternal aunt was said to be underdeveloped sexually and to be a habitual aborter.

Physical Examination.—The patient was a large well-developed 3-year-old, apparent male, with a height of 39¾ in. and a weight of 38 lb. (84th percentile for boys for both height and weight). The child had a well-developed musculature, particularly of the shoulder girdle. Other pertinent physical findings were limited to the genitalia. There was a moderate amount of thin long dark curly pubic hair. The phallus measured approximately 6 cm. in length and 7 cm. in circumference and had been circumcised. The urethral meatus was at the tip of the glans in normal position. No testes were palpated in the scrotum or in the inguinal canals.

Laboratory Findings.—Blood cell count and urinalysis were normal. Roentgenograms of the wrist showed a bone age of 7 years, as compared with

Submitted for publication Nov. 1, 1957.

From the Department of Pediatrics, University of Utah College of Medicine.

Appearance of phallus and internal genitalia during exploratory laparotomy. Note the ovaries, tubes, and uterus.

a chronological age of 3 years. Urinary 17-ketosteroid excretion was 32.8 mg/24 hours. Plasma 17-hydroxycorticosteroid levels (by the method of Nelson and Samuels) were undetectable, and there was no increase following the administration of 25 mg. of corticotropin (ACTH) intramuscularly.[4] Urinary 17-hydroxycorticosteroid excretion was 0.05 mg/24 hours, a value considerably below normal.[6]

Hospital Course.—The initial impression was that this child was a boy with macrogenitosomia praecox associated with congenital adrenal hyperplasia. However, the absence of palpable testes prompted further exploration and study of the child's genital and urinary tracts. On May 6, 1955, an explanatory laporotomy was performed. Uterus, tubes, and ovaries were identified, and it was felt by the surgeon that the right adrenal gland was hyperplastic. The biopsy specimen was taken from the left gonad, and microscopic examination revealed ovarian tissue with many primitive follicles.

After surgery, the parents were consulted as to their desires for the sex role to be assigned this child and chose to rear her as a girl. Studies then were undertaken to determine the feasibility of amputation of the phallus. Inspection of the bladder by cystoscopy revealed the mucosa to be normal throughout, the ureteral orifices to be in their normal position, and the trigone and bladder neck to be normal. Inspection of the prostatic urethra demonstrated, in the position usually occupied by the verumontanum, an irregular mass of tissue which was much larger than the normal verumontanum and which appeared to have an orifice within it. A ureteral catheter was passed through this opening and methoidal (Skiodan) sodium was injected; x-rays revealed a hollow viscus resembling a normal vagina. The impression of the urologists was that the vaginal orifice was in the position usually occupied by the verumontanum.

Following the cystoscopy procedure the child was dressed as a girl and prepared psychologically for the procedure of amputation of the phallus, which was performed on May 20, 1955. The postoperative course was uneventful. Since discharge from the hospital the patient has been maintained on cortisone therapy. She has accepted the change in sex role surprisingly well, despite the late age at which this change was accomplished.[6]

Comment

This patient represents the fourth reported case of female pseudohermaphroditism in which the external genitalia were so masculinized that the patient was indistinguishable from a boy with bilateral cryptorchidism.[1-4] Three of these patients had congenital adrenal hyperplasia, and one was a female pseudohermaphrodite without congenital adrenal hyperplasia.[4] Even a partial phallic urethra is not common in the pseudohermaphrodite. Only 24 cases have been reported in the literature, and only 10 of these have had congenital adrenal hyperplasia. Five of the latter group were reported recently by Reilly et al.[1] Their patients, with the exception of one who had been reported previously,[2] had various additional genital abnormalities. In each case the phallus was small and did not appear as a fully developed penis; chordee was present in all; secondary urethral openings were present in two, and a ventral opening of the urethra along the phallus was noted in some. There were various degrees of fusion and corrugation of the labia majora.

In the present case the clinical diagnosis of congenital adrenal hyperplasia was based upon the high urinary 17-ketosteroid excretion, the low plasma levels of 17-hydroxycorticosteroids, and the failure to produce elevations of these levels by the administration of a standard dose of corticotropin and the low urinary excretion of 17-hydroxycorticosteroids. The knowledge that a sibling also was a female pseudohermaphrodite was of aid in the establishment of the diagnosis, as were the advanced bone age and history of salt-craving.

Testes usually are present in the scrotum of the boy with congenital adrenal hyperplasia and usually are normal in size or somewhat small in comparison with the size of the phallus. It was the absence of palpable testes in this patient which prompted further investigation of the genital tract and the eventual determination of her true sex. This case emphasizes the necessity for definitive studies for determination of sex in the apparently cryptorchid male with precocious somatic and sexual development. Chromosome analysis of the buccal mucosa or of a skin biopsy specimen may be of aid, but the definitive diagnosis can be established only by demonstration of female internal genitalia on exploratory laparotomy.

Summary

A case of female pseudohermaphroditism due to congenital adrenal hyperplasia with complete masculinization of the external genitalia to resemble a cryptorchid male with macrogenitosomia praecox has been presented. This represents the fourth such case to be reported and the first of these to be diagnosed during life.

Department of Pediatrics, University of Utah, 1940 S. 2d East.

REFERENCES

1. Bentinick, R. C.; Lisser, H., and Reilly, W. A.: Female Pseudohermaphrodism with Penile Urethra, Masquerading as Precocious Puberty and Cryptorchidism, J. Clin. Endocrinol. 16:412, 1956.

2. Matheson, W. J., and Ward, E. M.: Hormone Sex Reversal in a Female, Arch. Dis. Childhood 29:23, 1954.

3. Perloff, W. H.; Conger, K. B., and Levey, L. M.: Female Pseudohermaphroditism: Description of 2 Unusual Cases, J. Clin. Endocrinol. 13: 783, 1953.

4. Ely, R. S.; Raile, R. B.; Bray, P. F., and Kelley, V. C.: Studies of 17-Hydroxycorticosteroids: IV. Evaluation of a Standard ACTH-17-Hydroxycorticosteroid Response Test in Children, Pediatrics 13:403, 1954.

5. Ely, R. S.; Ainger, L. E.; Seely, J. R.; Done, A. K., and Kelley, V. C.: Studies of 17-Hydroxycorticosteroids: X. Urinary Excretion of 17-Hydroxycorticosteroids in Patients with Rheumatic Fever, J. Clin. Endocrinol. 15:523, 1955.

6. Money, J.; Hampson, J. G., and Hampson, J. L.: Hermaphroditism: Recommendations Concerning Assignment of Sex, Change of Sex, and Psychological Management, Bull. Johns Hopkins Hosp. 97:284, 1955.

7. Reilly, W. A.; Hinman, F., Jr.; Pickering, D. E., and Crane, J. T.: Phallic Urethra in Female Pseudohermaphrodism, A. M. A. J. Dis. Child., to be published.

The Coil-Spring Sign and Intramural Hematoma of the Proximal Small Intestine

KENNETH F. SWAIMAN, M.D.; JILL F. ROOT, M.D., and RICHARD B. RAILE, M.D., Minneapolis

Introduction

The presenting complaint of abdominal pain is not infrequently a great problem to the diagnostician. The addition to the literature of any seemingly pathognomonic sign or finding that can be of aid in diagnosis deserves promulgation.

In 1954 Felson and Levin [1] described the x-ray finding of the "coil spring sign of the duodenum," which they noted in four of their cases and one previously described case [2] to be associated with intramural hematoma of the second and third portions of the duodenum. At the time of their article the five cases were the only reports of intramural hematoma of the duodenum (or small intestine) in the literature with adequate descriptions of roentgenological findings.

The case presented adds another confirmed instance of association of this sign with intramural hematoma of the proximal small intestine.

Historical Background

Probably the first case of intramural hematoma of the proximal small intestine with obstruction was described in 1893.[3] The case was that of a 49-year-old man who had a history of episodic vomiting and epigastric pain. The patient died of dehydration. The necropsy report states that "behind the duodenum, and involving the whole of the second part and nearly the whole of the first part, was a tumor of the size and shape of a kidney, which proved to be a false aneurysm situated between the mucosa and muscular coats of the bowel on its posterior aspect."

Since that time, approximately 20 cases of intramural hematoma of the proximal small intestine have been reported. About 60% of these cases have occurred in patients of the pediatric age group. There were several reports just after the turn of the century,[4,5] but there was then a lapse until the early 1930's.[6,7] Not until Liverud [2] published his case in 1948 were there any roentgenological studies of this condition. In 1952 Dey [8] reported two cases of intramural duodenal hematoma, one of which he briefly discussed. The case was that of a 6-year-old girl with a two-day history of abdominal pain and vomiting. No x-ray findings were mentioned. An intramural hematoma was found at operation in the wall of the first and second portion of the duodenum. In 1953 Stirk [9] reported a case of subserosal duodenal hematoma, of probable traumatic origin, in a 9-year-old boy. The hematoma resulted in duodenal obstruction. Diagnosis was established at surgery. No x-ray barium studies were mentioned.

In 1954 Magladry and Mathewson [10] reported a case of intramural duodenal hematoma secondary to trauma in a 9-year-old girl. They did not describe their x-ray findings in any detail but stated that there was narrowing of the second part of the duodenum. Diagnosis was proved by abdominal exploration. Also in 1954, Lampert, Goodfellow, and Wachowski [11] reported a case of traumatic subserosal hemorrhage of the proximal portion of the

Received for publication Oct. 18, 1957; accepted Oct. 24.

Surgical aspects of this case have been reported by Snider.[10]

From the Departments of Pediatrics, Minneapolis General Hospital and The University of Minnesota.

jejunum. The injury was sustained by a 15-year-old boy during a basketball game. Upper gastrointestinal barium studies revealed widening of the distal duodenum with slight obstruction near the ligament of Treitz. Films taken 72 hours after the initial examination revealed complete high jejunal obstruction. No coil-spring sign was seen. At operation a subserosal hematoma obstructing the jejunum at the ligament of Treitz was found and drained.

Since the cases reported by Felson and Levin [1] there have been three new cases, besides the present case, reported. One case, reported by Melamed and Pantone,[12] was considered by the authors to represent obstruction secondary to intramural duodenal hematoma, but no operative or postmortem proof was available to them. There was an obstructive lesion demonstrated roentgenologically in the third portion of the duodenum, but no coil-spring sign was present. However, because there are cases in the literature of duodenal obstruction secondary to retroperitoneal hematoma without intramural hematoma,[3,13] the possibility exists that their patient may not have had this lesion.

In 1956 White and Wollenman [14] reported a case of subserosal hematoma of the jejunum in association with duplication of a segment of the jejunum and a concomitant angiomatous vascular supply in "loose, myxomatous appearing serosal connective tissue." Accompanying barium studies do not reveal a "spring sign" to be present.

In 1957 Moody [15] reported a case of a 9-year-old boy with intramural hematoma of the jejunum caused by trauma. An upper gastrointestinal barium series revealed a coil-spring sign in the proximal jejunum. The diagnosis was suspected preoperatively from the x-ray picture. At operation there was a subserosal hematoma of the first portion of the jejunum just distal to the ligament of Treitz.

Report of Case

A 10-year-old boy was admitted for the first time to Minneapolis General Hospital on Nov. 24, 1954. He had been well until two days prior to admission, at which time he was sent home from school because "he looked sick." At home he began to vomit. The frequency of vomiting began to increase markedly over a period of several hours. The emesis was initially white and mucoid; later, the emesis consisted almost entirely of bile. There was an associated steady right upper quadrant pain. The pain began to increase in severity. It was consistently located in the same area and did not radiate. The urine had become scant and dark over the previous days. He had had no bowel movements for three days. His last bowel movement was normal in every respect. The past medical history was noncontributory to his present illness.

Examination revealed a quiet, cooperative, but alert white boy in no apparent acute distress. His blood pressure was 110/80; temperature, 98.6 F; pulse rate, 120 and regular; respirations were 20 per minute. Marked dehydration was present. The skin was dry and of poor turgor. The buccal mucosa and lips were dry and pale. Examination of the eyes, ears, and nose was unremarkable. There was no significant lymphadenopathy. The lungs were clear to percussion and auscultation. The heart was normal in size; no murmurs were heard. Examination of the abdomen revealed the liver to be palpable 4 cm. below the right costal margin. It was tender and somewhat tense. The spleen and kidneys were not palpable. No bowel sounds were heard. There was also diffuse epigastric tenderness to direct palpation. Rectal examination was normal. Neurological examination yielded nothing of note.

During the next day he was hydrated by means of intravenous fluid therapy. He continued to vomit everything taken orally. He was stoical, but on occasion he complained of mild epigastric pain and tenderness.

Admission laboratory work revealed a hemoglobin of 15.6 gm. per 100 cc.; white blood cell count of 16,600, with 94% polymorphonuclear cells, 5% lymphocytes, and 1% monocytes. The sedimentation rate was 3 mm. in an hour. Urinalysis revealed a faint trace of albumin and a specific gravity of 1.031. Microscopic examination was normal.

Three days after admission a history of a severe epigastric blow incurred in the course of a football game, three days before admission, was elicited. At the time of the blow the patient experienced a marked weakness, with severe epigastric pain radiating to his back. He was forced to leave the game and went home without mentioning the incident to his parents. On successive physical examinations it became apparent that the previously described hepatomegaly was in reality the liver

Fig. 1.—Intramural hematoma involving the distal duodenum.

Fig. 2.—Demonstration of the coil-spring sign.

augmented by an 8×8 cm. firm tender right upper quadrant mass.

A subsequent upper gastrointestinal series revealed a puddling effect in the third portion of the duodenum immediately followed by a "distended impression of contrast material as if in distended bowel with almost a coil-spring effect as is seen in intussusception." (There was some delay in emptying.) The conclusion of the radiologist was "marked distortion of duodenum probably on a traumatic basis." Excretory urograms and retrograde pyelograms revealed probable deviation laterally of the superior portion of the right ureter.

In view of the persistence of vomiting, the abnormal x-ray picture, and the discovery of the palpable mass, an exploratory laparotomy was performed. At operation displacement of the transverse colon revealed an 8×12 cm. hematoma of the wall of the third portion of the duodenum which extended into the retroperitoneal space (Fig. 1). Drainage of the hematoma was decided against, and the incision was closed. The patient was returned to the ward in good postoperative condition. Over a period of hours, on the third postoperative day, a gastric tube was slowly manipulated past the obstruction to facilitate tube feedings. After another week the hematoma had been sufficiently reabsorbed to enable the patient to tolerate oral feedings. From that time, he made a progressive, uneventful recovery.

An upper gastrointestinal series on Dec. 29, 1954, one month after admission, revealed "very definite changes in the contour and of the caliber of the descending portion of the duodenal loop. This, however, is an improvement over earlier studies." On May 2, 1954 (six months later) a repeat series revealed very definite improvement, but there was incomplete resolution of the intramural hemorrhage at that time.

Roentgenological Findings.—Figures 2 and 3 reveal the thickened mucosal folds which are first noted as the duodenum is filled with barium. The barium then appears in an area of apparent luminal widening associated with a smooth-walled intramural mass. In this same region the valvulae conniventes are seemingly forced together and in this way produce a striking coil-spring effect outlined with barium. There is no concomitant shortening of the duodenum. This configuration is occasionally seen in intussusception of the small bowel. However, in intussusception there is an accompanying shortening of the bowel associated with an inner lumen of small caliber.

Etiology

Intramural hematoma of the proximal small intestine has been reported in conjunction with blood dyscrasias (hemorrhagic purpura,[4,7] hemophilia [5]), pancreatic tumor,[6] duplication of the jejunum,[14] and trauma. Certainly trauma appears to be the leading

Fig. 3.—Demonstration of the coil-spring sign.

cause of this entity. Seven of the eight cases with associated "spring sign" were due to trauma, and the eighth case may possibly have been associated with an unknown injury.

Apparently the fixation of the distal duodenum by the ligament of Treitz predisposes this area to injury, because it can be forced against the spine, with probable compression of the adjacent mesenteric attachments.[1,16,17]

Felson and Levin [1] filled a closed loop of normal human small intestine removed at autopsy with barium suspension. They then injected the subserosal space of this intestine with water and hoped to simulate the clinical x-ray lesion. The coil-spring effect was not produced, but swelling of the mucosal folds along with a similar intramural lesion resulted.

Conclusion

Although the coil-spring sign is absent in some of the above-mentioned cases, the demonstration of this sign, at least for the present time, can well be considered pathognomonic of intramural hematoma of the proximal small intestine.

Summary

A case of an 11-year-old boy with an intramural duodenal hematoma induced by trauma is presented. The finding of the "coil-spring sign" was demonstrated. The previously reported cases with associated coil-spring sign are recorded.

Also included is a brief summary of the sparse literature regarding intramural hematoma of the proximal small intestine.

Department of Pediatrics, The University of Minnesota Medical School (14).

REFERENCES

1. Felson, B., and Levin, E. J.: Intramural Hematoma of the Duodenum: A Diagnostic Roentgen Sign, Radiology 63:823 (Dec.) 1954.

2. Liverud, K.: Hematoma of Jejunum with Subileus, Acta radiol. 30:163 (Aug.) 1948.

3. Perry, E. C., and Shaw, L. E.: On Diseases of the Duodenum, Guy's Hosp. Rep. 50:171, 1893.

4. Sutherland, G. A.: Intussusception and Henoch's Purpura, Brit. J. Dis. Child. 1:23 (Jan.) 1904.

5. Khantz, A., cited by Liverud.[2]

6. Oppenheimer, G. D.: Acute Obstruction of the Duodenum Due to Submucous Haematoma, Ann. Surg. 98:192 (Aug.) 1933.

7. Gamsteadt, E.: Invagination iliaque dans un cas de purpura de Henoch, Acta chir. scandinav. 73:280, 1933.

8. Dey, D. L.: Acute Duodenal Obstruction Due to an Intramural Haematoma, M. J. Australia 1: 708 (May 24) 1952.

9. Stirk, D. I.: A Case of Subserous Duodenal Haematoma, Brit. M. J. 1:712 (March 28) 1953.

10. Magladry, G. W., Jr., and Mathewson, C., Jr.: Duodenal Obstruction Due to Trauma, Stanford M. Bull. 12:205 (Aug.) 1954.

11. Lampert, E. G.; Goodfellow, J. G., and Wachowski, T. J.: Traumatic Subserosal Hemorrhage Causing Small Bowel Obstruction, Ann. Surg. 140:768 (Nov.) 1954.

12. Melamed, M., and Pantone, A. M.: Hematoma of the Duodenum: A Case Report, Radiology 66:874 (June) 1956.

13. Strachan, F. J.: Traumatic Obstruction of the Duodenum—Operation Recovery, Brit. M. J. 2:592 (Oct. 16) 1920.

14. White, R. J., and Wollenman, O. J.: A Case of Intestinal Obstruction from Spontaneous Subserosal Hemorrhage with Angiomatous Malformation Associated with Reduplication of the Jejunum, Ann. Surg. 143:720 (May) 1956.

15. Moody, E. E.: Acute Jejunal Obstruction Secondary to Traumatic Intramural Hematoma, Pediatrics 19:863 (May) 1957.

16. Estes, W. L.: Nonpenetrating Trauma of the Abdomen, Surg. Gynec. & Obst. 74:419 (Feb.) 1942.

17. Counseller, V. S., and McCormack, C. J.: Subcutaneous Perforation of the Jejunum, Ann. Surg. 102:365 (Sept.) 1935.

18. Snider, H. R.: Acute Duodenal Obstruction Secondary to Intramural Hematoma, Surgery 39: 860 (May) 1956.

Progress in Pediatrics

Acute Tubular Necrosis in Infancy and Childhood

GEOFFREY C. ROBINSON, M.D., F.R.C.P. (C), and LEI CHING WONG, M.D., Vancouver, B. C., Canada

Introduction

Acute renal failure is a clinical syndrome characterized by the sudden onset of severe oliguria or anuria followed by the retention of excretory products. It may be due to either reversible or irreversible lesions in the kidneys or urinary passages. In the majority of cases the lesion is reversible, provided an early diagnosis is made and appropriate management is instituted. Cases which prove to be irreversible may be very difficult to diagnose as such during life, particularly during the early course of the syndrome, and consequently they often merit essentially the same plan of management as the former group.

Acute tubular necrosis is now recognized as an important cause of acute reversible renal failure. For many years the existence of acute renal failure due to a variety of different etiological agents had been recognized.[1] During the past 15 years, it has been established that degeneration in the epithelium of the renal tubule is the lesion common to these cases of acute renal failure.[2] Likewise, similar pathogenetic mechanisms have been found to be involved in these diseases.[3,4]

As a result of these advances, a new rationale of management of acute renal failure has evolved, which is based on the fact that the renal lesion is reversible and survival depends upon prevention and control of complications during the period of renal dysfunction. Swann and Merrill[5] have aptly stated: "It cannot be said that this is a disease from which the patient usually recovers in spite of the physician. Rather it is a disease of which patients frequently die because of mismanagement."

Acute renal failure due to acute tubular necrosis in infants and children is the subject of this paper. The English-speaking pediatric literature is reviewed, and one case is reported. The management of the disorder is discussed, and one case of acute renal failure presumably due to acute tubular necrosis is reported. The renal failure was due to exposure to the vapors of a cleaning fluid containing carbon tetrachloride.

Report of a Case

A 20-month-old girl was admitted to St. Paul's Hospital, Vancouver, on April 14, 1952, for investigation of intractable vomiting and drowsiness of three days' duration. On April 9, she was playing in a small, poorly ventilated room while her father was cleaning a suit with "Aristocratic Spot Removing Fluid," which later was found to be pure carbon tetrachloride. They were exposed to the vapor for about one hour. Next day she was feverish and anorectic. On April 11, her temperature was 104 F; she began vomiting and passed some dark urine. During the next two days "a scant amount of urine" was passed, and she continued to vomit. She was admitted to a local hospital on April 13 and received a large volume of sodium-containing fluids parenterally. During that day she became unusually drowsy.

Because of continuing fever, vomiting, and unexplained drowsiness, she was transferred to St. Paul's Hospital on April 14 for investigation. On admission, her temperature was 101 F. Blood pressure was 95/60. She was very drowsy but responded to her name. She was jittery, and intermittent twitchings of the muscles of the face and extremities were noted. There was periorbital edema.

Submitted for publication Aug. 16, 1957; accepted Sept. 5.

Assistant Professor (Dr. Robinson), and Research Fellow (Dr. Wong), Department of Pediatrics, Faculty of Medicine, University of British Columbia.

Initial laboratory investigations revealed the following values: hemoglobin 10 gm. per 100 ml.; white blood cells, 9000 per cubic millimeter; nonprotein nitrogen, 138 mg. per 100 ml.; carbon-dioxide-combining power, 25 mEq. per liter; serum sodium, 138 mEq. per liter; serum chloride, 91 mEq. per liter; serum potassium, 5 mEq. per liter; serum calcium, 9 mg. per 100 ml., and serum phosphorus, 5.6 mg. per 100 ml. The urine had a specific gravity of 1.009, gave acid reaction, and contained albumin, red blood cells, and occasional white blood cells, but no casts. The spinal fluid was normal.

The hospital course can be divided into the oliguric and diuretic stages and the convalescence.

Oliguric Stage.—During the first 24 hours it was noted that the child voided only once. On the second hospital day edema became more generalized and she was extremely irritable when disturbed. Her blood pressure was raised to 115/80. Generalized clonic convulsions occurred on the second, third, and fourth hospital days. Repeated injections of 25% magnesium sulfate in a dose of 2 cc. every six to eight hours were given intramuscularly to reduce the blood pressure, with temporary effect.

On the third hospital day her serum chemistry studies showed hyponatremia (122 mEq. per liter) and hypochloremia (75 mEq. per liter), and 3% hypertonic saline, 125 cc., was given. This was followed by congestive heart failure, and she was digitalized.

At this time it was noted that her serum was icteric. The combination of hepatic and renal signs prompted consideration of carbon tetrachloride intoxication, and the history of exposure was then obtained.

Oliguria persisted for the first 10 days in the hospital. Throughout this period she was very drowsy, at times almost comatose. The blood pressure and nonprotein nitrogen rose steadily during this stage. On the ninth hospital day her blood pressure was 180/120 and the nonprotein nitrogen was 176 mg. per 100 ml. Acidosis and gradual rise of serum potassium were also noted from the early part of the oliguric stage. The serum potassium level reached 6.1 mEq. per liter on the ninth hospital day. Intestinal lavage was considered, but, fortunately, diuresis began the following day.

Restriction of fluid intake and accurate recordings of intake and urinary output were carried out as soon as the diagnosis of acute renal failure due to carbon tetrachloride intoxication became apparent, on the third hospital day. Fluids were given chiefly by vein because oral feeding was invariably followed by vomiting and diarrhea.

Diuretic Stage.—Diuresis began on the 10th hospital day, 15 days after the exposure. For the ensuing two days the patient became brighter when awake and spontaneous and purposeful activity increased. Hypertension persisted.

As soon as diuresis set in, the serum potassium level fell to normal and the low levels of serum sodium and serum chloride noted immediately preceding diuresis rose to normal. Azotemia and acidosis were still present.

On April 30, five days after the onset of diuresis, the patient's condition suddenly deteriorated and she became comatose again. Her temperature rose, and respiration became labored. This episode was preceded by numerous loose watery stools following the institution of oral feedings. Once again intravenous administration of fluids was resorted to. Although the plasma volume deficit secondary to the diarrhea was carefully replaced by adequate fluid, oliguria was again present on May 2, 3, and 4. During this period her condition was desperate. Hypernatremia, hyperchloremia, and hypokalemia were noted, and the nonprotein nitrogen, which had been leveling off three days after the onset of diuresis, rose again. After 10 days of this unexpected set-back, her general condition gradually improved. She was able to retain small amounts of oral feedings. Throughout this stage hypokalemia and hypocalcemia persisted and additional potassium and calcium were given. The nonprotein nitrogen returned to a normal level one month after admission.

Convalescence.—The remainder of the hospital stay was less dramatic and was characterized by gradual return of consciousness, although certain neurological deficits became apparent. Ataxia was severe at first, but she was able to walk out of the hospital with assistance 60 days after admission. In this connection it may be relevant that she had received 0.5 gm. of streptomycin daily from April 21 to April 30 and she was hard of hearing. Her vision was poor, and right internal strabismus was noted. The blood pressure gradually subsided to normal levels about two months after the onset of the present illness. The urine was normal at the time of discharge.

The late course in hospital was complicated by urinary-tract infection due to Proteus vulgaris. Frequent blood transfusions were required throughout the hospital stay because of marked anemia.

Three months after her original admission, she developed serum hepatitis, from which she recovered uneventfully.

Subsequent Course.—The patient was readmitted to St. Paul's Hospital at the age of 4 years, 26 months after the onset of acute renal failure, for surgical correction of the squint. At this time she still had mild ataxia. She had a severe hearing loss and was not speaking, apart from a few

words. Her intelligence was difficult to assess. Urinalysis and serum chemistry values were within normal limits. The blood pressure was normal.

Comment.—This case is typical of many reported in the literature. The presenting complaints of fever, vomiting, and drowsiness overshadowed the urinary suppression. When this was recognized and the icteric serum was observed, the history of exposure to carbon tetrachloride was obtained.

Because of the usual delay in recognition of oliguria, excess fluids were administered during the early oliguric stage. This resulted in a sequence of further complications.

Review of the Literature

General Considerations.—The clinical syndrome of acute tubular necrosis has been recorded since the 19th century.[6] However, it was not until 1941, after the report of Bywaters and Beall,[7] that widespread interest began to develop. These authors described the renal failure and renal tubular lesions in patients with crushing injuries. They also recognized that a few of these patients made a complete recovery of renal function.

Since that time, major contributions have been made to the understanding of the pathogenesis and pathology of the condition.[2,8-11] The clinical course of the syndrome has been studied,[5] and medical management has been discussed repeatedly.[12-15] Although numerous case reports have appeared in the medical, surgical, urological, and obstetrical literature in the last 10 to 15 years, only occasional case reports without a comprehensive review have appeared in pediatric journals. Our experience suggests that the syndrome is not so rare in infants and children as the paucity of reported cases would suggest.

We propose to review the literature of acute renal failure due to acute tubular necrosis in infants and children with regard to the etiology, clinical manifestations, clinical course, and outcome of the reported cases.

Selection of Cases.—We have confined this review to cases of acute renal failure due to acute tubular necrosis following sudden known insult to the kidney and also to certain cases of acute renal failure of unknown cause in which the clinical, laboratory, and autopsy findings were compatible with the diagnosis of acute tubular necrosis. In each case the infant or child had been previously well and free of any known prior renal disease. At times it was extremely difficult to decide upon an exact diagnosis in children, because of the high percentage of cases with no demonstrable precipitating cause. Several typical reported cases of this disease were reluctantly omitted from the study because of lack of sufficient data. Some other cases were excluded because of uncertainty regarding the influence of other factors in the pathogenesis of renal failure.

The cases included in the review are summarized in Tables 1 and 2.

Etiology.—Acute tubular necrosis has been described in various circumstances. According to Peters,[3] some 34 different agents have been found to cause this clinical syndrome. Wagner[16] grouped the different causes into 11 headings in order of their frequency: transfusion reaction; poisonings, including mercuric bichloride, carbon tetrachloride, and sulfonamides; posthemorrhagic and obstetric causes; post-traumatic shock; burn; infusion of distilled water; crush injuries; diarrhea; vomiting and dehydration; blackwater fever; paroxysmal hemoglobinuria, and hepatorenal failure. Waugh[4] divided the cases into five main groups: blood destruction; dehydration, shock, and electrolyte disturbance; tissue destruction; acute nephritis in pregnancy, and acute nephrosis in poisoning.

The etiology and the outcome of the reported cases in infants and children are presented in Table 3. It is apparent that in the pediatric age group nephrotoxic agents account for more than half of the reported cases. The high percentage of cases of unknown cause is of interest.

TABLE 1.—*Cases of Acute Renal Failure Due to Tubular Necrosis of Known Etiology*

Case No.	Year of Publication	Author	Age of Patient, Yr.	Cause	Duration of Oliguria, Days	Outcome
1	1941		2	Bismuth	10	Recovered
2		McClendon	15/12	Bismuth	5	Recovered
3		Erganian et al.	9/12	Sulfonamide	3	Died
4	1943	Press et al.	3/12	Sulfonamide	5	Died
5			5/12	Sulfonamide	3	Died
6		Dintenfass	3½	Sulfonamide	3	Recovered
7	1945		4	Sulfonamide	2	Recovered
8		Boyette	2	Bismuth	5	Died
9	1946	Goodpaster et al.	9	Burn	2	Died
10			2	Burn	3	Died
11		Petersilge	2	Bismuth	8	Recovered
12	1947	Dunsky	17/12	Potassium bromate	3	Died
13		Redish et al.	8	Sulfonamide	9	Recovered
14			10/12	Sulfonamide	15	Recovered
15	1948	Pratt	18/12	Sulfonamide	3	Recovered
16		Hoffman et al.	21/12	Bismuth	13	Recovered
17	1949	Thompson et al.	2½	Potassium bromate	3	Recovered
18		Swan et al.	3	Potassium bromate	9	Recovered
19	1950	Warren et al.	2/12	Potassium bromate	38	Recovered
20		Riddell	10	Incompatible transfusion	9	Recovered
21	1951		20/12	Sulfonamide	2	Recovered
22		Karelitz	6	Bismuth	7	Recovered
23		Zuelzer et al.	2 wk.	Hemolytic anemia	?	Died
24	1953	Kaplan et al.	5	Mercuric bichloride	6	Recovered
25	1955	Present authors	20/12	Carbon tetrachloride	10	Recovered
26			13	Incompatible transfusion	3	Recovered
27	1957	Carter et al.	14	Meningococcemia & shock	12	Recovered

Sulfonamide intoxication is the major nephrotoxic agent which causes acute renal failure in the present series. Erganian et al.,[17] in 1943, reported the case of a 9-month-old infant (Case 3) who died with acute oliguria due to administration of sulfadiazine. Autopsy disclosed sulfonamide crystals at the orifices of the ureteropelvic junctions, and tubular necrosis was found in the microscopic sections. Press et al.,[18] in the same year, reported two cases (Cases 4 and 5) of sulfathiazole intoxication with acute renal insufficiency in small infants, 3 months and 5 months old. These two infants developed hematuria, albuminuria, oliguria, hypertension, and azotemia two and three days after the institution of sulfathiazole therapy. One died five days later; the other, three days later. Autopsy did not reveal any sulfonamide crystals but showed marked degeneration of renal tubules, which contained eosinophilic casts. In 1948, Pratt[13] studied nine cases of acute anuria with azotemia. Two of them (Cases 14 and 15) were due to sulfadiazine intoxication.

TABLE 2.—*Cases of Acute Renal Failure Due to Acute Tubular Necrosis of Unknown Etiology*

Case No.	Year of Publication	Author	Age of Patient, Yr.	Duration of Oliguria, Days	Outcome
28			?	4½	Recovered
29			?	4	Recovered
30	1948	Pratt	?	2½	Recovered
31			?	3	Recovered
32			2½	8	Died
33			11/12	5	Died
34	1951	Zuelzer et al.	3/12	3	Died
35			6/12	2	Died
36	1954	Wagner	4	5	Recovered
37	1955	Mateer et al.	11½	5	Recovered

TABLE 3.—*The Etiology and Outcome of the Reported Cases of Acute Tubular Necrosis in Infants and Children*

Causes	Cases, No.	Outcome	
		Recovered	Died
1. Sulfonamide intoxication	9	6	3
2. Bismuth intoxication	6	5	1
3. Potassium bromate intoxication	4	3	1
4. Mercuric bichloride intoxication	1	1	
5. Carbon tetrachloride intoxication	1	1	
6. Burn	2		2
7. Incompatible transfusion	2	2	
8. Hemolytic anemia	1		1
9. Infection and shock	1	1	
10. Unknown	10	6	4
Total	37	25	12

He proposed a conservative therapeutic program which was designed to control the volume of body fluids and maintenance of extracellular electrolyte composition.

Sulfamerazine was recorded as a cause of acute renal failure by Dintenfass [20] (Cases 6 and 7) and also Riddell [21] (Case 21). Redish et al.[22] reported a case of prolonged anuria due to sulfathiazole (Case 13). Spontaneous diuresis occurred after nine days of anuria. No crystals were found in the urine. The blood sulfonamide level on the first day of anuria was only 2 mg. per 100 ml.

The second commonest nephrotoxic agent is bismuth. In 1941, McClendon [23] reported two cases (Cases 1 and 2) of bismuth intoxication, both of whom recovered after a long duration of oliguria. Other cases of bismuth intoxication with acute renal failure were reported by Boyette [24] (Case 8), in 1946; Petersilge [25] (Case 11), in 1947; Hoffman et al.[26] (Case 16), in 1949, and Karelitz et al.[27] (Case 22), in 1951. Thiobismol was used for the treatment of Vincent's angina in each case. Boyette's patient died 13 days after the administration of bismuth. In this case, decapsulation was performed after seven days of anuria. Five days later the infant was voiding adequately, but he died suddenly. At postmortem examination bifid ureter and aberrant vessel were found on the left side and an infarct was noted in the left kidney. Widespread tubular degeneration was found microscopically. In this case, overzealous administration of fluid during the anuric stage undoubtedly jeopardized the outcome.

Potassium bromate, which was the main chemical ingredient of the neutralizing solution after "cold wave" or "Toni Permanent Wave," has been reported as a cause of acute tubular necrosis by Dunsky [28] (Case 12), in 1947; Thompson et al.[29] (Case 17), in 1949; Swan et al.[30] (Case 18), in 1949, and Warren et al.[31] (Case 19), in 1950. The 17-month-old infant reported by Dunsky died three days after ingestion of the poison. Postmortem examination showed generalized anasarca and degeneration of the renal tubules. The 2-month-old infant reported by Warren et al. developed anuria after being inadvertently fed with "Toni Neutralizer." In spite of the age of the child, the duration of oliguria (4 days of complete anuria and 34 days of oliguria), and the degree of azotemia (blood urea rose to 360 mg. per 100 ml.), the survival of the patient adequately demonstrated the success of well-planned medical management.

Kaplan et al.[32] reported a case (Case 24) of acute renal failure due to mercuric bichloride intoxication. Cation-exchange resins were used in the treatment of this case.

Goodpaster et al.[33] reported two cases (Cases 9 and 10) of extensive burns followed by oliguria and azotemia. Both patients died, two and five days after injury. Postmortem examination showed extensive degeneration of tubules, which contained pigmented casts. Martineau and Hartman,[34] in their study of renal lesions in extensive cutaneous burns, included 10 cases (out of 20) in the pediatric age group. The ages ranged from 2 to 10 years. The burned areas were extensive and varied from 25% to 70%. The survival time ranged from 7 hours to 26 days. Those dying in the early stage showed marked tubular degeneration with only minimal or no congestion of the glomeruli. Those dying in the later stage showed tubular degeneration as well as cellular infiltration of the glomeruli. No clinical data were recorded.

Incompatible blood transfusion resulting in acute renal failure has been described repeatedly in adults. Riddell [21] reported a case (Case 20) in a 10-year-old child who made a complete recovery after nine days of severe oliguria. Carter et al.[35] have recently described a hemolytic transfusion reaction in 13-year-old boy (Case 26). Hemodialysis was performed on the eighth post-transfusion day, and recovery ensued. Wahle and Muirhead [36] recently reported a fatal case of acute renal failure after an incompatible blood transfusion. The clinical picture was that of intravascular hemolysis.

Autopsy revealed extensive bilateral cortical necrosis. This illustrates the difficulty in differentiating the reversible from the irreversible kidney lesions early in the course. The primary illness was a severe burn, which could have caused damage to the kidney before the transfusion reaction.

Zuelzer et al.[38] reported a 2-week-old infant (Case 23) with fulminating hemolytic anemia of unknown cause. The autopsy revealed severe tubular degeneration affecting particularly the distal segments of the nephron.

Carter et al.[35] have reported a 14-year-old boy (Case 27) with fulminating meningococcemia, shock, and acute tubular necrosis. Dialysis was done three times, and the patient recovered.

It is important to realize that acute reversible renal failure may exist without any demonstrable known cause, and this is particularly true in small infants. In these instances, the problem of differential diagnosis of acute pyelonephritis and acute glomerulonephritis always arises. This can be illustrated by the case reported by Buerger et al.[37] in 1949. An 8-month-old infant suddenly developed pallor, hypertension, anuria, and azotemia. Very small amounts of urine obtained on catheterization revealed albumin, red blood cells, and white blood cells. Initial urine culture grew Escherichia coli. Decapsulation and repeated peritoneal irrigations reduced the nonprotein nitrogen from 178 mg. to 36 mg. per 100 ml. Unfortunately, the child died 32 days after the onset of anuria. In spite of extensive chemotherapy and treatment with antibiotics, postmortem revealed pronounced pyelonephritis, ureteritis, and interstitial nephritis. There were severe degenerative changes in the tubules.

Pratt's[13] four other cases (Cases 28, 29, 30, 31) of acute anuria with recovery are included in the review. The ages of these patients and the cause of anuria were not mentioned.

Zuelzer et al.,[38] in their comprehensive study of 40 cases of circulatory diseases of the kidneys in infancy and childhood, included 5 fatal cases of lower nephron nephrosis. One case (Case 23) has been included in the group of known causes. In the four other cases (Cases 32, 33, 34, 35) no apparent cause was obtained from the case history. Accidental poisoning was suspected, but it could not be proved.

Wagner[16] described a case (Case 36) of acute renal failure of unknown etiology with complete recovery after five days of anuria. The author also discussed the cause of the associated anemia which is invariably seen in the syndrome.

In 1955, Mateer et al.[39] reported a case (Case 37) of acute tubular necrosis with complete recovery in an 11½-year-old child. The cause of acute renal failure was not apparent. Hemodialysis was used in the treatment of this patient.

The following cases are of interest, but they do not meet our criteria for the diagnosis of acute tubular necrosis and are reluctantly excluded from the study.

A fatal case of acute renal failure was reported by Higgins et al.[19] in 1951. A 26-month-old child, after receiving 36 gm. of sulfasuccidine in a period of three days for gastroenteritis, suddenly developed anuria which lasted for 10 days. The blood urea rose to 316 mg. per 100 ml. Decapsulation of the kidney to promote urine formation was ineffective; peritoneal dialysis was performed, and gradual onset of diuresis ensued. However, blood urea never returned to normal, and three months later the child died with uremia. Postmortem examination revealed advanced damage to the parenchyma of the kidneys. The etiological importance of the sulfasuccidine is difficult to assess. Because the renal lesion noted at autopsy is ill defined, this case was excluded from the series.

Schwartz et al.[40] in 1951 reported an interesting case of acute renal failure of unknown etiology. Their case presented a typical clinical and chemical picture. Exchange transfusion was performed because of hyperkalemia. Unfortunately, the patient

died one hour after the procedure. No autopsy was obtained, and hence this case was excluded.

Jonsson[41] described three newborn infants who presented a clinical picture of acidosis, anuria, albuminuria, and azotemia following asphyxia at birth. One of them died, and the postmortem examination revealed numerous heme casts in the distal renal tubules, the type found in lower nephron nephrosis. However, epithelial degeneration of the renal tubules was not described, and hence the case is not included. The other two cases diagnosed as lower nephrone nephrosis due to asphyxia neonatorum were not included because of uncertainty of the pathogenesis of the renal lesion.

Clinical Manifestations.—Age Distribution: The age and the outcome of the reviewed cases are summarized in Table 4. Over 40% of the cases are between 1 and 4 years, the age group with the highest incidence of accidental poisoning, and it is interesting that poisoning is the major cause of acute tubular necrosis in the reported cases. The mortality is highest among infants aged less than one year.

Presenting Complaints: No uniform pattern of initial clinical manifestations exists. Anuria was the commonest presenting symptom, this being the case in 18 instances. In a few cases it was accompanied by other problems, such as vomiting, shock, convulsions, and somnolence.

In most of the cases the patients were hospitalized 24 to 36 hours after the onset of anuria. In Case 7 anuria had been present for two days, but the child was not admitted and spontaneous return of urinary function occurred. Marked oliguria was the first manifestation of acute renal failure in the two cases of extensive burns (Cases 9 and 10).

TABLE 4.—*Age Distribution and the Outcome of the Reported Cases of Acute Tubular Necrosis in Infants and Children*

Age of Patients, Yr.	Cases, No.	Result	
		Recovered	Died
Under 1	9	2	7
1 to 4	16	12	4
5 to 14	8	7	1
Unknown	4	4	
	37	25	12

Vomiting was the presenting complaint in 11 cases, and in 2 of the cases it was associated with diarrhea. In the cases of acute renal failure due to potassium bromate and mercuric bichloride, vomiting occurred very soon after the ingestion of the poison, and intractable vomiting was the presenting problem in the case of carbon tetrachloride intoxication.

Convulsions were encountered in six cases. In all of them anuria had been present for one to five days; however, the patients were not hospitalized until convulsions occurred. It seems probable that convulsions following the onset of anuria are usually a complication of excess fluid administration in the anuric stage.

Edema itself was the presenting sign in two cases. In one of these (Case 18) the child had not voided for six days, although he was not hospitalized until pulmonary edema developed. In the other case generalized edema was the presenting complaint in an oliguric child.

Somnolence followed by anuria 12 hours later was noted in a case of bismuth poisoning.

Jaundice was the presenting sign in a fatal case of fulminating hemolytic anemia.

Duration of Oliguria and Anuria: The duration of the oliguria and anuria varied from 2 days (Cases 7, 9, 21, and 35) to 38 days (Case 19). In this series the duration of oliguria was not closely related to the mortality.

The average duration of oliguria was 3 to 5 days, although it was 5 to 10 days in 11 cases and longer than 10 days in a few cases.

Complete anuria was present in 18 of 37 cases, and in most of them it lasted for 36 hours. However, in five cases it lasted for 2 to 3 days and in seven cases, from 4 to 11 days. This observation is in contrast

to that of Swann and Merrill,[5] who have pointed out that complete anuria is rare in acute renal failure in adults.

Complications: 1. Hypertension. Hypertension was found very early in the oliguric stage. This is in agreement with observations in adults. Elevation of both systolic and diastolic blood pressures on initial examination was recorded in 15 of 37 cases. Three cases showed no elevation of blood pressure at any time, and in the other cases it was not recorded.

2. Pulmonary edema and congestive heart failure. Pulmonary edema was a common complication in the fatal cases of the present study. This was more often a pathological finding than a clinical one, and further attention will be given to this point in the section dealing with the fatal cases. Congestive heart failure was recorded in two cases (Cases 16 and 25).

3. Uremic syndrome. Meroney et al.[42] drew attention to the relationship between the onset of clinical uremia and the plasma nonprotein nitrogen level and stated that the clinical picture of lethargy, mental confusion, and severe vomiting developed when the nonprotein nitrogen reached 250 mg. per 100 ml. In the present series it was not possible to confirm any definite relationship. In Case 11 the child remained rational throughout the entire course, even when the nonprotein nitrogen was 240 mg. per 100 ml., on the sixth day of anuria. On the other hand, Case 36 was very drowsy on the second day of oliguria, when the blood urea was 516 mg. per 100 ml., and was comatose when it reached 596 and 704 mg. per 100 ml. In Case 18 the child was "extremely ill, acidotic and uremic" on the sixth day of anuria, at which time the blood urea nitrogen was 170 mg. per 100 ml.

In other cases alterations in consciousness developed at low levels of nonprotein nitrogen, and it may well be that causes other than uremia were responsible. In Case 8 the child lapsed into profound drowsiness and began to vomit on the ninth day of anuria, when the nonprotein nitrogen was 120 mg. per 100 ml. Next day diuresis began, and two days later, when the nonprotein nitrogen was 61 mg. per 100 ml., she was able to sit up and take oral feeds. In Case 12 an infant of 17 months became stuporous on the second day of oliguria, when the nonprotein nitrogen was only 103 mg. per 100 ml. Another infant of the same age (Case 15) lapsed into coma on the fourth day of anuria, when the nonprotein nitrogen was only 64 mg. per 100 ml.

4. Anemia. Anemia is a common finding in acute renal failure, and pallor was an important sign in this series of cases.

5. Infection. Respiratory infection during the latter part of the oliguric stage or during the diuretic stage was recorded in two cases. Urinary tract infection during convalescence was noted in our case.

6. Jaundice. Jaundice was noted during the oliguric stage in three cases. In one of these, jaundice was due to acute hemolytic anemia. The other two were cases of bismuth and carbon tetrachloride poisoning.

Laboratory Data.—1. Azotemia. In all reported cases the initial study showed azotemia. There was no constant pattern of the nonprotein nitrogen concentration in relation to the different stages of acute renal failure in the present study. In most of the cases azotemia steadily increased with the duration of oliguria or anuria. In a minority of cases the nonprotein nitrogen was maintained at the same level throughout the oliguric stage.

In the diuretic stage, in six cases the nonprotein nitrogen returned to normal in 10 days and in seven cases, in 20 days after the onset of diuresis.

In two cases the nonprotein nitrogen was normal in 39 and 65 days, respectively, and in two cases it was still abnormal after 4 and 2½ months.

2. Carbon-dioxide-combining power. The initial level of carbon-dioxide-combining power was recorded in 22 cases, and in all except 3 cases it was markedly reduced. The lowest recorded level was 6.7 mEq. per liter (Case 18).

3. Sodium and chloride. Hyponatremia and hypochloremia were recorded in seven cases during the oliguric stage. In four other cases only hypochloremia was recorded, no mention being made of serum sodium concentration. The lowest levels were recorded in Case 15, with serum sodium 108 mEq. per liter and serum chloride 67 mEq. per liter. In this case hypertonic saline, 1.5%, was used. Hypertonic 5% saline was given to the patient in Case 14 when the serum sodium was 128 mEq. per liter and the serum chloride, 97 mEq. per liter. In Case 25, hypertonic 3% saline was used when serum sodium was 125 mEq. per liter and chloride was 80 mEq. per liter.

The concentration of serum sodium and chloride during the diuretic stage was reported in very few cases.

The serum sodium and chloride concentration remained normal during diuresis in Cases 14, 16, and 19.

Prognosis.—In the present review, 12 of 37 cases died during the course of acute renal failure. Most of the deaths (10 cases) occurred during the oliguric stage.

One significant finding in these fatal cases was edema, in the form of pulmonary or cerebral edema or generalized anasarca. This was recorded in 11 cases. One can not be sure whether this complication was the cause of death, although it can be said that the affected children had all received an excessive amount of fluid during the oliguric stage.

Other complications found at postmortem examination included extensive hemorrhages in the skin and bronchopneumonia in one case (Case 8). Toxic myocarditis was found in Case 12.

Differential Diagnosis

It may be difficult to establish the cause of acute renal failure, and this is particularly the case in infants and small children, in whom the etiology may not be obvious. There should be no problem, however, in cases in which the history points to a clinical situation known to precede acute tubular necrosis. A knowledge of the chemical agents which cause this renal lesion is important, and parents must be specifically asked if their child has been exposed to or had access to poisons.

Oliguria and anuria due to dehydration, with or without salt depletion, are frequently seen in infants and small children. In the great majority of such situations repair of the extracellular volume results in a prompt return of urine formation. To distinguish between oliguria due to dehydration and acute renal failure, when doubt exists, a catheter should be inserted into the bladder and an intravenous infusion of 5% dextrose in water, 350 ml. per square meter, should be given in 60 minutes.[48] The rate of urine flow should be checked gainst the normal values for age, noted in Table 5.[49] Prompt return of flow to normal excludes acute renal failure.

In cases of acute renal failure in which the cause remains obscure, management should be based on the assumption that a reversible renal lesion exists. Under such circumstances consideration should be given to the following conditions in differential diagnosis.

1. *Other Primary Renal Diseases.*—Acute Glomerulonephritis: Oliguria or anuria may be the presenting and dominating problem in this condition and may persist for weeks.[44] The history of preceding upper respiratory illness in a child over 3 years of age and a latent interval of apparent recovery, followed by mild constitutional symptoms, mild edema, and dark urine, usually precede the urinary suppression. Hypertension is more marked at the onset of the oliguria than in acute tubular necrosis. The urine tends to be grossly bloody, with marked proteinuria and many

TABLE 5.—*Satisfactory Hourly Urine Output*

Age, Yr.	Urine Output, Ml
Birth to 1	8–20
1 to 5	21–25
6 to 10	26–30
11 to 14	31–50
More than 14	51–100

cells and casts in the sediment. The persistence of an acid urine and urinary specific gravity near 1.020 favor the diagnosis of acute glomerulonephritis. It is important to note, however, that Swann and Merrill [5] found urinary specific gravity 1.015 to 1.020 (corrected for protein) during the first few days in proven cases of acute tubular necrosis.

Acute Pyelonephritis: The case reported by Buerger et al.[37] of an 8-month-old infant who suddenly developed acute renal failure demonstrates how this disease may imitate acute tubular necrosis. In older children the history of fever, chills, flank pain, and dysuria with marked pyuria should point to the correct diagnosis. The importance of obtaining a catheter urine specimen for culture in cases of acute renal failure is emphasized.

Hemorrhagic Papillary Necrosis: This condition, usually seen in adult diabetics and associated with urinary obstruction, has been described in a 2-month-old infant,[45] and one of us has recently seen a similar case. Again, the importance of initial catheter sample for both diagnosis and therapy is emphasized.

2. *Obstructive Uropathies.*—Acute renal failure may be due to either acute or chronic obstructive lesions of the urinary tract.[46] Such lesions may be due to congenital stricture of the urethral meatus or posterior urethral valves, congenital or acquired vesical neck obstructions, bilateral intrinsic or extrinsic ureteral obstructions, and obstructions of the urinary tract by sulfonamide crystals.

The vast majority of these uropathies present as problems of urinary infection or chronic renal insufficiency rather than as acute renal failure. The only obstructive lesion causing acute renal failure which we have encountered in our review is the ureteral obstruction due to sulfonamide drugs.

Particular attention to the history of prior urinary disease is indicated in all cases of acute renal failure. In occasional cases cystoscopy and retrograde studies are indicated.

Sulfonamide crystalluria. The importance of sulfonamide drugs as a cause of acute renal failure has been noted in Table 3. Renal damage may be produced by tubular degeneration or by obstruction of the upper or lower urinary tract by crystals. When the latter possibility exists, cystoscopic examination and ureteral catheterization are indicated.

3. *Renal Vascular Lesions.*—Zuelzer et al.[38] have reported a group of rare circulatory diseases of the kidney. While some of these conditions cannot be diagnosed during life, the following three deserve comment.

Bilateral symmetrical cortical necrosis. This condition may be exceedingly difficult to distinguish from acute tubular necrosis. It may occur at any age and in either sex and may follow conditions which usually set the stage for acute tubular necrosis. This is well demonstrated by the case reported by Wahle and Muirhead.[36] Severe diarrhea is a not uncommon precipitating illness. Zuelzer [38] has noted that bilateral symmetrical cortical necrosis is probably the commonest single cause of acute renal failure in infancy.

Occlusion of the renal artery. Renal infarction due to obstruction of one or both renal arteries has been described. The condition sometimes can be diagnosed during life if further evidence of emboli and infarction is present.

Thrombosis of renal veins. This condition is usually seen in association with dehydration and debilitating illness. The diagnosis may be suspected clinically if there is sudden enlargement of one or both kidneys together with characteristic urinary and chemical findings of acute renal failure. The occurrence of thrombosis in other veins is common. Recovery has been reported.

4. *Reflex Anuria.*—Reflex anuria following catheterization or operative manipulation of the organs of the urogenital system has been described.

Management

General Considerations.—There is no specific therapy. Treatment is based on the assumption that the renal lesion is reversible and that survival depends upon avoiding or controlling the various physiological derangements that ensue when renal function is impaired.

The importance of early recognition of oliguria or anuria cannot be overemphasized. The case reports in the literature contain several instances of late diagnosis of oliguria in which the patient was first seen in a state of overhydration due to excess water or water and salt administration. The possibility of acute renal failure must be considered in all circumstances when the known etiological mechanisms prevail. The commonest of these are nephrotoxic agents, states of severe shock and dehydration, and increased blood and tissue destruction.

In cases due to nephrotoxic agents the poison must be eliminated. Gastric lavage may be indicated in cases of accidental ingestion. Dimercaprol (BAL) may be lifesaving in mercuric bichloride intoxication, and prompt institution of therapy is important. High fluid intake and alkalinization of the urine are recommended for the prevention of renal damage by the sulfonamides. Some authors recommend alkalinization following hemolytic transfusion reactions.[51]

In some cases the primary condition causing the acute renal failure will result in severe shock due to depletion of plasma volume. In such cases, prior to the obvious development of oliguria, the lost blood or fluid should be replaced. The timing of this replacement is of great importance and may prevent or reduce serious renal damage.

The severity and duration of the individual case of acute tubular necrosis is variable, but it is prudent to initiate a comprehensive and long-range therapeutic plan in each case as soon as the diagnosis is established. In mild cases, simple restriction of water, sodium chloride, potassium, and protein, together with the provision of adequate calories, as carbohydrate, will result in a favorable outcome. However, in the majority of cases the therapeutic result depends on careful daily assessment of fluid, electrolyte, nitrogen, and caloric balance by an experienced team of medical, nursing, and laboratory workers.

In all cases where the history and clinical state of the patient suggest acute renal failure, the following routine is recommended.

1. Initial Body Weight: This determination is frequently neglected in the confusion of the admitting procedure. It is of prime importance for planning of future fluid therapy.

2. Catheterization and Urine Collection: The initial catheter urine should be examined immediately for reaction, specific gravity, albumin, and microscopic appearance, and a specimen should be obtained for culture. Accurate determination of output in female infants is very difficult, but it is of great importance in guiding the course of therapy. A small Foley catheter should be left in the bladder in a female child, and a Penrose drain should be strapped to the penis in the male.

3. Blood Pressure: The initial blood pressure determination should be carefully obtained. It may be low and indicate shock. A normal reading will serve as a standard for subsequent anticipated elevation. A practical point in the infant and small child concerns the use of a suitable size of cuff. Too big or too small a cuff will give findings of considerable error, and the same cuff should be used for repeated measurements.

4. Venipuncture: Serum chemistry studies should include determination of nonprotein nitrogen, serum sodium, chloride, potassium, and carbon-dioxide-combining power. Serum calcium and phosphorus are also of considerable value. These findings serve not only as indices of renal dysfunction but also as a base line for therapy. Severe anemia may be present at the onset or may develop during the course of the disease, and

initial measurements of hemoglobin and red count, at least, are important.

5. Discontinue Intake: Once the diagnosis is clearly established, it is wise to discontinue oral intake temporarily until the plan of treatment is defined. The significance of restriction of fluid must be explained to all nursing attendants.

6. Sedation: Sedation with barbiturates is desirable in cases with central nervous system stimulation.

7. Records: Careful daily record should be kept of weight, urine output and fluid intake, blood pressure, and laboratory determinations. The general trend of events can be anticipated in advance, and on the basis of daily revision of all the relevant data appropriate changes in therapy can be made.

It has been shown above that the clinical course comprises two distinct stages, each with its own complications and therapeutic problems, and the management of these stages will be discussed in detail below.

The Anuric Stage.—1. Water and Electrolyte Balance: The anuric kidney cannot excrete water. Attempts to "open up the kidneys" by "forcing fluids" merely result in retention of water and gain in weight. Excess water administration with resultant hypotonicity of body fluids is the most serious complications during this stage. It is easier to prevent than to treat. Diuretic agents, which function by decreasing the tubular reabsorption of filtered water, are not effective.

The usual method of planning water intake from the anticipated losses from stool, urine, skin, and lungs for the succeeding 24 hours has to be revised when renal water output is drastically reduced. It is practical to supply the volume of urine passed in the preceding 24-hour period plus average insensible loss for age less an average value for water of oxidation. These values are noted in Table 6, modified from Talbot et al.[52] Stool losses are negligible in the absence of diarrhea and vomiting.

TABLE 6.—*Daily Water Requirements for Patients with Anuria*

Age, Yr.	Dose, Ml./m.²/Day
<2	1,000
2–8	700
>8	400

Daily body weight is a valuable guide for following water balance. A gradual fall in weight is desirable, and weight gain should occasion concern. For a small infant weighing should be done at the same time every day and under the same conditions of dress.

A serum sodium level above 130 mEq. per liter is an indication of good control of water balance. A rapid fall below this figure together with a gain in weight means excess water intake and the danger of water intoxication. There is a minimal loss of sodium and chloride from lungs and skin, and in the absence of vomiting or diarrhea these losses can be disregarded. If gastrointestinal losses of any magnitude occur, they must be replaced.

Increased tissue catabolism, muscle injury, infection, and hemolysis all result in release of cell potassium, and, since its excretion is primarily renal, hyperkalemia will ensue. The danger of old banked blood as a source of exogenous potassium has recently been emphasized.[47]

Potassium excess and its effect on the heart is an important cause of death during this stage. It has recently been pointed out [42] that the concentrations of calcium and sodium in the serum influence the toxicity of hyperkalemia. Restoration of the serum calcium to normal levels antagonizes the effect of hyperkalemia. Raising the plasma sodium concentration to normal, in addition to depressing the serum potassium concentration, may also have an antagonistic effect similar to that of calcium.

The concentration of serum potassium should be correlated with the clinical situation and the concentration of serum calcium and sodium, and it is a safe policy to keep the concentration below 7.0 mEq. per liter in the oliguric stage. Restriction of intake

must be enforced, and the high potassium content of fruit juices must be recognized.[40] Likewise, endogenous protein catabolism must be reduced by oral or parenteral administration of dextrose.

The rapidly rising inorganic phosphate level is associated with hypocalcemia. Because calcium is a specific antagonist of potassium, the occurrence of hypocalcemia and hyperkalemia constitute an added risk to the patient's life. The tendency to tetany is offset by the associated acidosis. The hypocalcemia during this stage should be controlled by the administration of calcium by mouth or vein.

Invariably these patients develop a profound anemia, and repeated transfusions with carefully matched fresh blood should be given. The volume given should be subtracted from the daily fluid intake.

2. Nutrition: The provision of adequate calories is desirable but a difficult problem during this stage. The diet must be protein-free, and calories must be supplied as fat or carbohydrate. Table 7, modified from Hill,[53] outlines the approximate daily caloric requirements of a normal resting infant or child.

The caloric needs can be supplied if oral feeding is tolerated. The Bull diet,[54] a mixture of dextrose and peanut oil given orally or via an indwelling Levin tube, has been used with success. The formula for this diet is dextrose, 400 gm.; peanut oil, 100 gm.; acacia to emulsify, and water to 1 liter. This formula provides 2500 Cal. Lipomul-Oral (Upjohn) is another liquid preparation, which contains 40% vegetable oil and provides 120 Cal. per ounce. At times, and particularly in infants and small children, vomiting and diarrhea occur, with resultant additional losses.

TABLE 7.—*Approximate Daily Caloric Requirements of a Normal Resting Infant or Child*

	Daily Caloric Requirement Cal./Kg.
Young infants	60
Older infants	55
Children	30

In the event that parenteral feeding has to be resorted to, serious caloric deficits may arise. Carter et al.[35] recommend the administration of 40% invert sugar into the vena cava through a large indwelling catheter. If gastric suction is used as a means of effecting extrarenal excretion, the volume of water so removed may be resupplied as 25% dextrose by vein.[63]

3. Management of Complications: Water intoxication. This situation is commonly produced prior to the recognition of the diagnosis of acute renal failure. It should never be allowed to occur during the management of a known case. The serum sodium may fall to 120 mEq. per liter or even lower levels. The decision whether to treat the hyponatremia with hypertonic saline or to discontinue all intake and wait for water loss from skin and lungs to correct the imbalance is a most difficult one. Swann and Merrill[5] have recommended the latter course. However, if symptoms of water intoxication are marked, a trial of 50 to 100 cc. of 3% saline is justified. The use of hypertonic saline may increase the plasma volume and cause congestive heart failure and pulmonary edema. Once the signs of cardiac failure or pulmonary edema develop, the patient should be digitalized immediately. After digitalization has been completed, a daily maintenance dose is usually contraindicated because of the danger of digitalis poisoning.

Potassium intoxication. The gradual retention of potassium during acute renal failure should be carefully observed, and at levels of 6 to 8 mEq. per liter other procedures must be instituted. Conservative measures include administration of calcium gluconate intravenously, hypertonic dextrose and insulin intravenously, and cation-exchange resins.

Intravenous 10% calcium gluconate, 10 cc. twice daily, will temporarily correct the hypocalcemia and thereby lessen the danger of potassium toxicity to the heart.

The use of hypertonic dextrose and insulin[42] also will temporarily reduce hyper-

kalemia. We have used this combination in a 7-month-old infant with acute renal failure of unknown cause for six consecutive days to control the serum potassium level. The solution was made up as follows: 25% dextrose in water, 100 cc.; 10% calcium gluconate, 20 cc.; regular insulin, 10 units; ⅙ M sodium lactate, 20 cc. This infusion was run in slowly over a period of six to eight hours.

Cation exchange resins transfer potassium from the plasma to the intestine. Their action is slow, and they should be instituted early and in conjunction with the other two methods described above. Reports of their efficacy in adults are conflicting. Vomiting and fecal impaction have resulted from oral and rectal usage.[42] Strauss [15] points out a further disadvantage of potassium-free resins in use at present. The ammonium- and hydrogen-loaded resins increase acidosis, and the sodium-loaded resins may contribute to expansion of the extracellular fluid. Others report favorably on their efficacy in removing large potassium loads.[55-57] We have encountered only one report of their use in acute tubular necrosis in our review.[32] Rubin et al.[43] recommend ammonium carboxylic exchange resins, 10% solution, 100 ml. rectally every four hours as a retention enema.

In the event that hyperkalemia persists and electrocardiographic evidence of potassium intoxication is present, extrarenal excretion methods must be used. These include exchange transfusion, peritoneal and intestinal lavage, and use of the artificial kidney.

Exchange transfusions have been used by numerous workers.[40,58-61] The procedure is simple, but laborious, and the danger of old banked blood has been mentioned.

Intestinal lavage offers the important advantage that no special equipment or surgery is required. Using this method, we have encountered difficulty in regulating the amount and speed of the fluid introduced. Too rapid infusion resulted in profuse bloody diarrhea, and slow administration resulted in absorption of the fluid.

We have had no personal experience with peritoneal lavage or use of the artificial kidney in infants and children. The latter methods have been used in children.[30,35,39] For further discussion concerning choice of method the reader is referred to the papers by Strauss [15] and Carter et al.[35]

The uremic syndrome. As the anuric stage progresses, even when water and electrolyte balance is well controlled, the plasma nonprotein nitrogen will reach high levels. Meroney et al.[42] have noted that the uremic syndrome develops when the nonprotein nitrogen reaches 250 mg. per 100 ml. The patient becomes lethargic and drowsy and sometimes comatose. Vomiting and severe diarrhea may be present. In the presence of this picture, dialysis with one of the methods of extrarenal excretion is indicated.

Acidosis. The gradual fall in carbon-dioxide-combining power during the anuric stage usually does not necessitate specific management. The addition of sodium lactate to the day's intravenous fluid has been recommended by Meroney et al.[42]

Hypertension. This does not appear to present a dangerous problem during the anuric stage. Temporary reduction in blood pressure follows the use of intramuscular magnesium sulfate.

Infection. These patients are prone to cross infections, and every effort must be made to prevent this problem. During the period of parenteral infusion, oral hygiene is important. The buccal mucosa must be cleansed regularly to prevent serious mouth infections. The danger of sulfonamide drugs and streptomycin in renal failure has been recognized.[62] These drugs are contraindicated during the oliguric stage.

The Diuretic Stage.—Continued observation during this stage is important, and the tendency to relax must be avoided. Serial observations of daily body weight and, if possible, daily urine collections should be continued. Twice weekly determinations of the hemoglobin concentration and red cell count and more frequent estimations of serum electrolytes, nonprotein nitrogen, and

carbon-dioxide-combining power should be continued for at least two weeks. Problems of water and electrolyte balance continue to present a therapeutic challenge, and to this may be added the complications of undernutrition, infection, severe anemia, and, at times, delayed healing of wounds.

1. Water and Electrolyte Balance: Urine volume may increase slowly or with great rapidity. The polyuria can be explained in part by defective tubular reabsorption of electrolytes and the inability to form a concentrated urine, but it may also be due to added solute loads resulting from nitrogen and potassium retention and any excess of sodium administered early in the oliguric period.[5] In addition, these patients are often overhydrated at this stage, and restoration of normal body water content and composition necessitates a period of negative water balance. If the water and electrolyte excess is disregarded and the water and electrolyte losses are quantitatively replaced, the polyuria will continue. The object is to avoid dehydration secondary to obligatory polyuria and at the same time permit negative water balance. Water intake should cover the usual basic insensible and renal needs, allowing a high figure for the latter in view of indifferent concentrating ability. The previous day's urine volume should not be replaced. If dehydration develops, the fluid intake should be increased.

Sodium and chloride are lost in the early diuretic stage, owing to defective tubular function, and hyponatremia and hypochloremia associated with dehydration and peripheral vascular collapse may occur. This can be rapidly corrected by giving appropriate water and electrolyte solutions and temporarily increasing the daily water and electrolyte allowance. On the other hand, Swann and Merrill[5] have shown that urinary salt loss may in part be due to salt excess antedating the diuresis, and they have emphasized that replacement of these losses may perpetuate the diuresis. Sodium should not be quantitatively replaced; a daily allowance of 50 to 70 mEq. per square meter should be provided. Serial blood chemistry studies should be a guide to impending electrolyte disturbance and should influence the trend of therapy. A gradual fall in weight during the early diuretic stage should be expected.

The development of hypernatremia and hyperchloremia associated with neurological signs has been described[48] early in the diuretic stage. Whether this is due to faulty tubular reabsorption of water or to excess salt administration during the oliguric stage is not generally agreed upon. If neurological signs are present, symptomatic therapy is indicated.

Potassium loss results in hypokalemia after the first few days of the diuretic stage. Serial potassium levels warn of impending trouble, and when the level of 3.5 mEq. per liter is reached oral potassium is given as fruit juices or as the chloride or citrate, 3 to 5 gm. daily.

Calcium loss with resultant hypocalcemia should not present a problem, because of the introduction of milk to the feeding.

2. Nutrition: After one to two weeks of the oliguric stage, undernutrition is marked in infants and small children. Weight loss may continue into the diuretic stage. Gradual resumption of oral feeding is urged in view of past experiences of severe vomiting and diarrhea. Protein foods should be gradually introduced as liquid and semisoft solids. Oral vitamins A, B, and D and ascorbic acid should also be provided.

3. Anemia: Continuing anemia should be watched carefully, and periodic blood transfusions should be given as indicated.

4. Infections: Infections may dominate the picture during this stage. Bronchopneumonia is a common complication, and infections secondary to poor oral hygiene during the period of total parenteral feeding must be actively treated. Urinary infection associated with prolonged catheterization also occurs and must be treated with the appropriate chemotherapeutic agents.

Summary

A case of acute renal failure due to acute tubular necrosis is reported. The syndrome followed exposure to carbon tetrachloride.

The literature of acute renal failure due to acute tubular necrosis in the pediatric age group is reviewed. The etiology, clinical manifestations, and outcome of reported cases are summarized.

The physiological derangements and management during the anuric and diuretic stages are discussed, and particular attention is given to the prevention and control of the complications which ensue when renal function is abruptly impaired.

Health Centre for Children, 715 W. 12th Ave.

REFERENCES

1. Osler, W.: Principles and Practice of Medicine, Ed. 2, New York, Appleton-Century-Crofts Company, 1895, p. 763.

2. Oliver, J.; MacDowell, M., and Tracy, A.: The Pathogenesis of Acute Renal Failure Associated with Traumatic and Toxic Injury, J. Clin. Invest. 30:1305, 1951.

3. Peters, J. P.: Oliguria and Anuria Due to Increased Intrarenal Pressure, Ann. Int. Med. 23: 221, 1945.

4. Waugh, D.: Acute Nephrosis: The Kidney of Acute Renal Failure, Am. J. M. Sc. 226:310, 1953.

5. Swann, R. C., and Merrill, J. P.: The Clinical Course of Acute Renal Failure, Medicine 32:215, 1953.

6. Ponfick, E.: Berlin. klin. Wchnschr. 20:389, 1883, cited by Waugh.[4]

7. Bywaters, E. G. L., and Beall, D.: Crush Injuries with Impairment of Renal Function, Brit. M. J. 1:427, 1941.

8. Lauson, H. D.; Bradley, S. E., and Cournand, A.: The Renal Circulation in Shock, J. Clin. Invest. 23:381, 1944.

9. Selkurt, E. E.: Renal Blood Flow and Renal Clearance During Hemorrhagic Shock, Am. J. Physiol. 145:699, 1946.

10. Lucke, B.: Lower Nephron Nephrosis, Mil. Surgeon 99:371, 1946.

11. Mallory, T. B.: Hemoglobinuric Nephrosis in Traumatic Shock, Am. J. Clin. Path. 17:427, 1947.

12. Kugel, V. H.: Management of Acute Toxic Nephrosis, Am. J. Med. 3:188, 1947.

13. Pratt, E. L.: Treatment of Anuria, Am. J. Dis. Child. 74:730, 1947.

14. Strauss, M. B.: Acute Renal Insufficiency Due to Lower Nephron Nephrosis, New England J. Med. 239:693, 1948.

15. Strauss, M. B., and Raisz, L. G.: Treatment of Acute Renal Shutdown, A. M. A. Arch. Int. Med. 95:846, 1955.

16. Wagner, J.: Acute Tubular Necrosis with Anaemia, Great Ormond St. J. 7:66, 1954.

17. Erganian, J. A., and Doval, J. A.: Fatal Anuria Following Administration of Sulfonamides with Reference to Tubular Necrosis and Regeneration, J. Lab. & Clin. Med. 28:808, 1943.

18. Press, E., and Kennerstein, M.: Additional Manifestation of Sulphathiazole Toxicity: Non-Calculous Renal Insufficiency Following the Use of Sulphathiazole, Arch. Dis. Childhood 18:50, 1943.

19. Higgins, T. T.; Williams, D. I., and Nash, D. F. E.: The Urology of Childhood, London, Butterworth & Co., Ltd., 1951, p. 33.

20. Dintenfass, A.: Allergic Manifestation to Sulfamerazine, with 2 Case Reports of Anuria in Children, Ohio M. J. 41:628, 1945.

21. Riddell, H. I.: The Lower Nephron Syndrome in Children, J. Urol. 65:177, 1951.

22. Redish, J.; West, J. R.; Whitehead, B. W., and Chase, H.: Abnormal Renal Tubular Back-Diffusion Following Anuria, J. Clin. Invest. 26: 1043, 1947.

23. McClendon, S. J.: Toxic Effects with Anuria from Single Injection of Bismuth Preparation, Am. J. Dis. Child. 61:339, 1941.

24. Boyette, D. P.: Bismuth Nephrosis with Anuria in Infant, J. Pediat. 28:493, 1946.

25. Petersilge, C. L.: Prolonged Anuria Following Single Injection of Bismuth Preparation, J. Pediat. 31:580, 1947.

26. Hoffman, W. S., and Marshall, D.: Management of Lower Nephron Nephrosis, Arch. Int. Med. 83:249, 1949.

27. Karelitz, S., and Freedman, A. D.: Hepatitis and Nephrosis Due to Soluble Bismuth, Pediatrics 8:772, 1951.

28. Dunsky, I.: Potassium Bromate Poisoning, Am. J. Dis. Child. 74:730, 1947.

29. Thompson, H. C., and Westfall, S. W.: Potassium Bromate Poisoning, J. Pediat. 34:362, 1949.

30. Swan, H., and Gordon, H.: Peritoneal Lavage in the Treatment of Anuria in Children, Pediatrics 4:586, 1949.

31. Warren, S. A., and Gross, W. V., Jr.: Clinical Recovery Following Prolonged Anuria in an Infant 2 Months of Age, Pediatrics 5:954, 1950.

32. Kaplan, S. A., and Fomon, S. J.: Function Recovery Pattern in Acute Renal Failure Following Ingestion of Mercuric Chloride, A. M. A. Am. J. Dis. Child. 85:633, 1953.

33. Goodpaster, W. E.; Levenson, S. M.; Tagnow, H. J.; Lind, C. C., and Taylor, F. H. L.: Clinical and Pathological Study of the Kidney in Patients with Thermal Burns, Surg. Gynec. & Obst. 82:652, 1946.

34. Martineau, P. C., and Hartman, F. W.: Renal Lesions in Extensive Cutaneous Burn, J. A. M. A. 134:429, 1947.

35. Carter, F. H.; Aoyama, S.; Mercer, R. D., and Kolff, W. J.: Hemodialysis in Children: Report of 5 Cases, J. Pediat. 51:125, 1957.

36. Wahle, G. H., Jr., and Muirhead, E. E.: Bilateral Renal Cortical Necrosis in a Child Associated with an Incompatible Blood Transfusion, Texas J. Med. 49:770, 1953.

37. Buerger, W. R.; Lambert, E. C., and Maitland, B. A.: Peritoneal Irrigation: Method of Treatment of Acute Renal Failure in an Infant, Am. J. Dis. Child. 78:237, 1949.

38. Zuelzer, W. W.; Charles, S.; Kurnetz, R.; Newton, W. A., Jr., and Fallon, R.: Circulatory Diseases of the Kidneys in Infancy and Childhood, A. M. A. Am. J. Dis. Child. 81:1, 1951.

39. Mateer, F. M.; Greenman, L., and Danowski, T. S.: Hemodialysis of the Uremic Child, A. M. A. Am. J. Dis. Child. 89:645, 1955.

40. Schwartz, R.; Tomsovic, E. J., and Schwartz, I. I.: Hyperpotassemia and Body Water Disturbance in an Anuric Child, Pediatrics 7:516, 1951.

41. Jonsson, B.: Lower Nephron Nephrosis in Asphyxia Neonatorum, Acta paediat. 40:401, 1951.

42. Meroney, W. H., and Herndon, R. F.: Management of Acute Renal Insufficiency, J. A. M. A. 155:877, 1954.

43. Rubin, M. I., and Calcagno, P. L.: Renal Disease in Infants and Children, Pediatrics 17: 781, 1956.

44. Whitelaw, W.: Case of Anuria Lasting 25 Days: Recovery, Lancet 2:460, 1877.

45. Tamaki, H. T., and Whitman, M. A.: Hemorrhagic Papillary Necrosis of the Kidney, J. A. M. A. 150:1304, 1952.

46. Keitzer, W. A.: Acute Uremia, J. Urol. 73: 920, 1955.

47. Teschan, P. E.; Post, R. S.; Smith, L. H., Jr.; Abernathy, R. S.; Davis, J. H.; Gray, D. M.; Howard, J. M.; Johnson, K. E.; Klopp, E.; Mundy, R. L.; O'Meara, M. P., and Rush, B. F., Jr.: Post-Traumatic Renal Insufficiency in Military Casualties: I. Clinical Characteristics, Am. J. Med. 18: 172, 1955.

48. Luetscher, J. A., Jr., and Blackman, S. S., Jr.: Severe Injury to Kidneys and Brain Following Sulfathiazole Administration: High Serum Sodium and Chloride Levels and Persistent Cerebral Damage, Ann. Int. Med. 23:741, 1943.

49. Barclay, T. L., and Wallace, A. B.: Management of Burns: II. Fluid Replacement in Burned Patients, Lancet 1:98, 1954.

50. Hall, A. D., and Luetscher, J. A., Jr.: Renal Disease, New England J. Med. 239:621, 1948.

51. Mollison, P. L.: Blood Transfusion in Clinical Medicine, Oxford, England, Blackwell Scientific Publications, 1951, p. 311.

52. Talbot, N. B.; Kerrigan, G. A.; Crawford, J. D.; Cochran, W., and Terry, M.: Application of Homeostatic Principles to the Practice of Parenteral Fluid Therapy, New England J. Med. 252:856, 1955.

53. Hill, F. S.: Practical Fluid Therapy in Pediatrics, Philadelphia and London, W. B. Saunders Company, 1954, p. 10.

54. Bull, G. M.; Jockes, A. M., and Lowe, K. G.: Conservative Treatment of Anuric Uremia, Lancet 2:229, 1949.

55. Elkinton, J. R.; Clark, J. K.; Squires, R. D.; Bluemle, L. W., and Crosley, A. P., Jr.: Treatment of Potassium Retention in Uremia with Cation Exchange Resin, Am. J. M. Sc. 220:547, 1950.

56. Knowles, H. C., and Kaplan, S. A.: Treatment of Hyperkalemia in Acute Renal Failure Using Exchange Resins, A. M. A. Arch. Int. Med. 92:189, 1953.

57. Evans, B. W.; Hughes-Jones, N. C.; Milne, M. D., and Yellowlees, H.: Ion Exchange Resins in the Treatment of Anuria, Lancet 2:791, 1953.

58. Bessis, M.: Use of Replacement Transfusion in Diseases Other Than Hemolytic Disease of Newborn, Blood 4:324, 1949.

59. Snapper, I., and Schaefer, L. E.: Treatment of 2 Patients with Hepatorenal Syndrome and Acute Renal Failure by Exsanguino Transfusion, Ann. Int. Med. 34:692, 1951.

60. Dausset, J.: Lower Nephron Nephrosis: Report of Treatment of 44 Patients by Repeated Replacement Tranfusions, Arch. Int. Med. 85:416, 1950.

61. Goldbloom, R. B.: Renal Failure with Extreme Hyperpotassemia: Its Treatment with Exchange Tranfusion, New England J. Med. 250: 717, 1954.

62. Keefer, C. S., and Hewitt, W. L.: The Therapeutic Value of Streptomycin: A Study of 3000 Cases, Ann Arbor, Mich., Edwards Brothers, Inc., 1948, p. 261.

63. Scribner, B. H.: Syllabus for the Course on Fluid and Electrolyte Balance, 1953, Fluid Research Fund, Seattle.

Abstracts from Current Literature

A. M. A. Archives of Internal Medicine, Chicago

99:536-672 (April) 1957

A Clinical Study in Hodgkin's Disease. Bernard Levinson, Bruce A. Walter, Maxell M. Wintrobe, and George E. Cartwright.—p. 501.

Cold Agglutinins in Listeria Monocytogenes Infections. Roy J. Korn, Vincent J. Yakulis, Catherine E. Lemke, and Bernhard Chomet.—p. 573.

* Treatment of Staphylococcic Endocarditis. Joseph T. Melton and Bruce Logue.—p. 581.

99:673-846 (May) 1957

The Sensitivities and Cross Resistances of Gram-Negative Bacilli to Antibiotics. Burton A. Waisbren and Carl L. Strelitzer.—p. 744.

* The Treatment of the Nephrotic Syndrome with Steroids in Children and Adults. Kurt Lange, Ruth Strang, Lawrence B. Slobody, and Eugene J. Wenk.—p. 760.

Eosinophilic Leukemia. Edward J. Fadell, Richard I. Crone, Maurice E. Leonard, and Manuel D. Altamirano.—p. 819.

Micrococcus Tetragenus Septicemia. Marjorie Lewisohn.—p. 824.

Treatment of Staphylococcic Endocarditis.—Staphylococcic endocarditis continues to be one of the most difficult and frustrating therapeutic problems in medicine. At one time Staphylococcus was responsible for only a small percentage of all cases of bacterial endocarditis, while now Staphylococcus is second in frequency only to Streptococcus. The authors report seven patients, of whom six were cured. Their schedule of treatment consisted of penicillin in massive doses given with intravenous continuous drip. The initial doses were in the range of 50,000,000 units, with booster doses of 1,000,000 units every six hours. In addition, they state, erythromycin, 500 mg. orally four times daily; streptomycin, 1 to 2 gm. intramuscularly daily, and probenecid, 0.5 gm. orally four times daily, should be given. If there was no response on this regimen within three days' time the dose of penicillin was doubled and the treatment was continued for four more days. If this schedule did not produce a clinical response, combinations of other antibiotics were given. They felt that the successful regimen should be continued for five to six weeks.

The Treatment of the Nephrotic Syndrome with Steroids in Children and Adults.—The authors report their study of 42 children and 19 adults with the nephrotic syndrome. They define the nephrotic syndrome as comprising the forms formerly called "lipid nephrosis" and the nephrotic stage of subacute glomerulonephritis. In 82% of children (42 cases) and 68% of adults (19 cases) complete diuresis was induced in the first attempt with large doses of corticotropin. In all except one case diuresis was complete when repeated attempts were made in cases of initial failure. Their recommended dosage for the induction of diuresis is 100 to 200 units of aqueous corticotropin (25 to 50 units q. 6. h.). Children under 40 lb. of body weight received 100 units, while heavier children received 160 units and adults received 200 units per day. Without further therapy after the initial induction of diuresis most cases relapsed or recurred with one year. Fifty per cent of the cases relapsed within six months. The authors started giving their patients large doses of oral cortisone five days after the onset of diuresis. The schedule consisted of giving the cortisone on three successive days of each week (300 mg. per day to children under 40 lb.; 400 mg. per day to all others) for one year. After that time, therapy was gradually terminated by prolonging intervals between maintenance courses. Under this regimen the mortality of 24 cases, observed up to 66 months, was reduced from the expected 5.64 deaths to 1 death.

American Heart Journal, St. Louis

54, No. 3 (Sept.) 1957

* Chest Deformity in Children with Congenital Heart Disease. George M. Maxwell.—p. 368.

Complete Transposition of the Aorta: Levoposition of the Pulmonary Artery with Pulmonary Stenosis. J. Bret and M. Torner-Soler.—p. 385.

Partial Anomalous Venous Connection. John C. Wood, Marcel E. Conrad Jr., and Andrew G. Morrow.—p. 422.

Anomalous Left Coronary Artery: Adult Type. August J. Jurishica.—p. 429.

54, No. 4 (Oct.) 1957

* Congenital Aortic Septal Defect. Julio A. Berreta, Isidro Perianes, Alfredo Buzzi, and Félix Fernández Madrid.—p. 548.

Corrected Transposition of Great Vessels. J. Albert Schaefer and Lionel A. Rudolph.—p. 610.

Congenital Valvular Stenosis of Pulmonary and Aortic Valves with Atrial Septal Defect. L. Horlick and J. E. Merriman.—p. 615.

Chest Deformity in Children with Congenital Heart Disease.—The genesis of chest deformity occurring in children with congenital heart disease is evaluated. It is generally felt that the chest deformities occurring in association with congenital heart disease are secondary to the cardiomegaly, but it is the author's contention that these deformities are rather the result of respiratory disease or, less often, dyspnea.

In the author's experience, chest deformity has occurred in those patients with congenital heart disease in whom respiratory infections are common. In isolated pulmonic stenosis and coarctation, where cardiac hypertrophy is common but respiratory infections do not occur with increased incidence, chest deformities have not been found.

The initial chest deformity to appear is Harrison's sulci. These grooves, appearing in association with respiratory infections, are "mobile" initially but, with repeated respiratory disease, become fixed by one year of age. The sulci give the chest an appearance of bulging, but the chest circumference is not actually enlarged and the normal head-chest ratio is maintained. The poor development and malnutrition commonly seen in patients with congenital heart disease tend to accentuate the appearance of bulging. With repeated respiratory infections, the deformity may progress over a variable period of time to the so-called "pigeon-breast" with sternal protrusion. This deformity remains fixed despite surgical correction of the cardiac lesion.

The author notes the similarity of the chest deformities of patients with congenital heart disease to those with chronic respiratory disease such as asthmatics and fibrocystics. Chest deformity due to other causes, just as vitamin deficiency and scoliosis, were excluded in the author's series.

Congenital Aortic Septal Defect.—Congenital aortic septal defect is a relatively rare congenital anomaly which may produce clinical signs indistinguishable from those of patent ductus arteriosus.

The authors present three cases of congenital aortic stenosis, all of which were diagnosed clinically as having patent ductus arteriosus but at the operating table proved to have aortic septal defects. The patients were 11, 44, and 22 years of age. The three cases had in common a continuous murmur present in the first and/or second intercostal spaces accompanied by a systolic or continuous thrill of maximal intensity in the same area. In one of the cases there was an apical protodiastolic murmur. X-ray studies revealed a normal cardiac shadow in the youngest of the three patients. One case revealed slight cardiac enlargement, a very prominent pulmonary artery and aortic knob, and augmented pulmonary markings. In the third case the heart was slightly enlarged, with dilatation of the ascending aorta, pulsatile hila, and augmented pulmonary markings. ECG was normal in one case and revealed evidence of left ventricular hypertrophy in the other two. Cardiac catheterization, done in two of the three cases, revealed a left-to-right shunt at the pulmonary artery level, but the catheter did not pass through the defect in either case. In neither case was there significant pulmonary hypertension.

The clinical feature which permits distinction of aortic septal defect from patent ductus arteriosus is the lower localization in the third and fourth intercostal spaces of the thrill and murmur in the former condition. Radiologically aortic septal defect is characterized by augmented pulsations in the ascending aorta rather than in the aortic knob as is the case in patent ductus arteriosus. Cardiac catheterization may serve to distinguish between the two conditions if the catheter crosses and thus localizes the defect.

None of the three cases had any of the distinguishing features of aortic septal defect, and, accordingly, all were referred for surgery as having patent ductus arteriosus. Because of the similarity between the two conditions, the authors conclude that errors in diagnosis can be avoided only if the cardiac catheter can be passed through the defect.

American Journal of Pathology, Ann Arbor, Mich.

33, No. 5 (Sept.-Oct.) 1957

A Cyst in the Primordium of the Tricuspid Valve of an Abnormal Human Embryo. James E. Kindred.—p. 967.

Streptococcal Cardiac Lesions in Rabbits. Joel G. Brunson, Peter E. Fehr, and Richard L. Davis.—p. 977.

*Acute Glomerulonephritis: A Histopathologic Study by Means of Thin Sections. Edith Grishman and Jacob Churg.—p. 993.

Acute Glomerulonephritis: A Histopathologic Study by Means of Thin Sections.—In a study of 21 cases of acute glomerulonephritis by means of thin (0.5μ) sections, the basic alteration was thought to be inflammation of the intercapillary mesangium. Early lesions were characterized by intracapillary leukostasis accompanied by swelling and some proliferation of endothelial cells. These were associated with mesangial edema and capillary ischemia. With progression of the process there were increased edema and infiltration by inflammatory cells, the latter predominantly mononuclear but including polymorphonuclear leukocytes. The glomerular lobules became ballooned, and the capillaries were spread and compressed. There was also some separation of the capillaries from the surface membranes, although the epithelial basement membrane remained largely intact. Fibers appearing in the mesangium in the later stages of inflammation became more obvious as the edema subsided, and this was interpreted as the transition to subacute glomerulonephritis. There was no consistent correlation between the histologic appearance and the clinical data, but in those cases characterized by the severest histologic changes the patients died in a state of azotemia.

American Review of Tuberculosis and Pulmonary Diseases, New York

76, No. 4 (Oct.) 1957

Effect of Pyridoxal on Uptake of C^{14}-Activity from Labeled Isoniazid by Mycobacterium Tuberculosis. Irene U. Boone, Verda G. Strang, and Betty S. Rogers.—p. 568.

* Changing Patterns in Childhood Tuberculosis. Rea M. Schneider and Eleanor E. Drummond.—p. 579.

Tuberculosis of the Superficial Lymph Nodes in Children: A Review with a Report of Experience of Enzymatic Debridement. Anastasios A. Anastasiades, Evangelos C. Tsikoudas, Edith M. Lincoln, and John F. Daly.—p. 588.

Comparison of a Simple Helium Closed with the Oxygen Open-Circuit Method for Measuring Residual Air. Hurley L. Motley.—601.

Enumeration of Viable Tubercle Bacilli from the Organs of Nonimmunized and Immunized Mice. John L. Sever and Guy P. Youmans.—p. 616.

Editorial: Natural Healing and Chemotherapy. O. Kanner and E. D. Peasley.—p. 669.

The Examination of Sputum: I. Collection and Selection. Joseph M. Kurung.—p. 671.

The Examination of Sputum: II. Search for Elastic Tissue. Joseph M. Kurung.—p. 675.

The Examination of Sputum: III. Search for Fungal Spores. Joseph M. Kurung.—p. 679.

Studies of Nontuberculous Acid-Fast Bacilli Recovered from Human Sources: I. Bacteriologic Studies. J. Carroll Bell and Dick K. Riemensnider.—p. 683.

Experimental Sensitization of Guinea Pigs with Candida Albicans and Adjuvants. Ralph A. Vogel and W. Krehl.—p. 692.

The Classification and Susceptibilities to Chemotherapeutic Agents of Chromogenic Acid-fast Bacilli. Marvin Rogul et al.—p. 697.

Relative Efficacies of Chick Embryo and Standard American Trudeau Society Medium in Isolation of Tubercle Bacilli from Human Sputum. Paul Bunn and Frances Robinson.—p. 703.

Indication for Adjuvant Corticotropin and Corticosteroid Therapy in Tuberculosis: A Statement of the Committee on Therapy.—p. 708.

76, No. 5 (Nov.) 1957

* BCG: Past, Present, and Future. Arvid J. Wallgren.—p. 715.

Report of Ad Hoc Advisory Committee on BCG to the Surgeon General of the United States Public Health Service.—p. 726.

The Effects of Early Isoniazid Treatment in Experimental Guinea Pig Tuberculosis. Lenore R. Peizer, Aaron D. Chaves, and Daniel Widelock.—p. 732.

Tubercle Bacillus Wax as an Experimental Vaccine Against Mouse Tuberculosis. Anson Hoyt, Richard L. Dennerline, Frederick J. Moore, and C. Richard Smith.—p. 752.

Bronchiectasis and Acute Pneumonia. William Ruberman, Irving Shauffer, and Thomas Biondo.—p. 761.

Tuberculous Hilar and Mediastinal Adenitis. D. N. Shivpuri and Bindra Ban.—p. 799.

The Current Status and Treatment of Lymphatic Tuberculosis. James M. Schless and James A. Wier.—p. 811.

Tuberculous Meningitis. Granville Nickerson, O. Morgante, P. N. MacDermot, and S. Graham Ross.—p. 832.

The Quantitative Determination of Isoniazid and Para-Aminosalicylic Acid in Body Fluids. John R. Maher, Jack M. Whitney, John S. Chambers, and David J. Stanonis.—p. 852.

Two Cases of Methemoglobinemia and Acute Hemolytic Anemia with Death Following the Ingestion of a Solution of Para-Aminosalicylic Acid. Francis X. Claps.—p. 862.

Preliminary Observations with the Use of Paper Electrophoresis in Studying Serum Protein Changes as an Index of Progress in the Tuberculous Patient. J. R. Harrower et al.—p. 892.

The Efficiency of Centrifugation as a Means of Concentrating Tubercle Bacilli from Sputum. Charles R. Webb et al.—p. 899.

Changing Patterns in Childhood Tuberculosis.—This study was initiated by the Los Angeles County Tuberculosis and Health Association when it was noted that, contrary to the trends in adult tuberculosis, the incidence of tuberculosis in children in 1954 and 1955 had risen in the State of California.

Incidence of childhood tuberculosis rose from 18 per 100,000 population in 1951 to 28 per 100,000 in 1955, with those in the birth to 4-year-old age group 54 per 100,000 in 1951 and 102 in 1955.

The most frequently reported form of the disease is primary infection. The type of patient has changed considerably. In 1951 the usual patient was an ill child with fairly extensive roentgenographic involvement, found because of symptoms. In 1955 search for tuberculosis revealed many asymptomatic children with some roentgenographic involvement. When diagnosis was made, there has been a tendency to treat these children with antimicrobial agents.

In spite of the rise in incidence of primary infections, there has been a fall in the incidence of complications, and the mortality rate has also decreased sharply.

BCG: Past, Present and Future.—First reports on the efficiency of BCG vaccination were based on studies that could not stand critical analysis and, therefore, the original BCG work was not taken seriously.

At present, there is rather unanimous agreement that an adequately performed BCG vaccination undoubtedly provides fairly satisfactory protection (*a*) against the immediate consequences of a tuberculous infection and against serious forms of primary tuberculosis and (*b*) against early postprimary diseases, miliary tuberculosis, and tuberculous meningitis, as well as against pleurisy and early postprimary pulmonary tuberculosis. The protection against late postprimary types of tuberculosis seems to be slighter and more uncertain.

BCG vaccination is not recommended for general use in a community where general prophylactic public health measures against tuberculosis are adequate, the morbidity rate is low, and the sources of infection are so rare that only a few children become infected at school age. However, it is indicated where the reverse of this is true, as well as in selected cases, such as tuberculin-negative pupil nurses or medical students, persons who work in hospitals for tuberculous patients, and small children who are uninfected contact cases in tuberculous families.

In the future, indication for general use of BCG vaccine will depend upon the degree of susceptibility of the population. In a population highly susceptible to tuberculosis, general use of BCG vaccine will be indicated; in a population with natural resistance so high that infection seldom occurs even in the most susceptible persons, BCG vaccination will be unnecessary, even for selected groups.

Bulletin of the Johns Hopkins Hospital, Baltimore

100, No. 5 (May) 1957

Atrio-Ventricular Defect of Membranous Septum: Left Ventricular-Right Atrial Communication with Malformed Mitral Valve Simulating Aortic Stenosis; Report of a Case. Charlotte Ferencz.—p. 209.

* Splenectomy in Hemophilia. James D. Gross et al.—p. 223.

100, No. 6 (June) 1957

* Hypertension Due to Unilateral Renal Disease: With a Report on a Functional Test Helpful in Diagnosis. Thomas B. Connor et al.—p. 241.

Studies on the Pathogenesis of Fever: VII. Comparative Observations on the Production of Fever by Inflammatory Exudates in Rabbits and Dogs. Robert G. Petersdorf and Ivan L. Bennett Jr.—p. 277.

101, No. 1 (July) 1957

Pneumococcal Pneumonia Treated with Penicillin and Aspirin. Robert G. Petersdorf et al.—p. 1.

* Fetal Blood Studies: VI. The Oxygen Capacity of Human Fetal Blood in Term Pregnancy and in Postmaturity. Harry Prystowsky and N. J. Eastman.—p. 45.

* Fetal Blood Studies: VII. The Oxygen Pressure Gradient Between the Maternal and Fetal Bloods of the Human in Normal and Abnormal Pregnancy. Harry Prystowsky.—p. 48.

101, No. 3 (Sept.) 1957

Studies on Rickets Induced by a Low Calcium Diet: Effect of Starvation, Citrates and Succinates. William C. Thomas Jr. et al.—p. 123.

101, No. 4 (Oct.) 1957

Electron Microscope Studies of Ferret Respiratory Cells Infected with Influenza. Gerhart Hotz and F. B. Bang.—p. 175.
The Etiology of Pharyngeal Diverticula. Victor E. Negus.—p. 209.

101, No. 5 (Nov.) 1957

Mechanism of the Hemolytic Anemia Induced by Nitrofurantoin (Furadantin): Further Observations on the Incidence and Significance of "Primaquine-Sensitive" Red Cells. Exall L. Kimbro Jr. et al.—p. 245.

Splenectomy in Hemophilia.—The authors report four patients who had splenectomy for hemophilia, with detailed postoperative coagulation studies on two patients. In addition, details are given of coagulation studies performed pre- and postoperatively on two hemophiliac dogs. It is the conclusion of the authors that splenectomy in hemophiliacs is both a dangerous and a frivolous procedure.

Hypertension Due to Unilateral Renal Disease: With a Report on a Functional Test Helpful in Diagnosis.—The authors describe a test which has proven to be extremely helpful in the diagnosis of hypertension due to unilateral renal disease. Details of the test and its possible pitfalls are described. In brief, the test consists of simultaneous collection of urine from both ureters (and bladder) and a measurement of the urine volume and sodium (and chloride) concentration from each ureter. A positive test occurs when the water volume and concentration of electrolyte are reduced in one kidney as compared with the other. A negative test occurs either when there is equal volume and concentration of electrolyte from each kidney or when there is a reduction in volume from one kidney but an increase in the concentration of electrolyte from the same side.

In the second part of the paper the authors describe histologic changes observed in kidneys in which there was unilateral renal disease causing hypertension, from which the authors formulate a pathological-physiological basis for hypertension. Their thesis is that hypertension occurs only when there is "ischemic" tubular atrophy, i. e., atrophy of tubular cells which remain viable. When there is total vascular necrosis or destruction of tubular cells secondary to pyelonephritis, for example, no unilateral hypertension will be expected to occur. The authors describe clinical and laboratory aids which will lead one to suspect the diagnosis of unilateral renal disease and also provide an indication for their test.

Fetal Blood Studies: VI. The Oxygen Capacity of Human Fetal Blood in Term Pregnancy and in Postmaturity.—The authors measured the oxygen capacity in a series of 142 infants, 88 of whom were born at 36 to 40 weeks of pregnancy and the remainder (54) at 41 to 45 weeks. In the two groups the average oxygen capacities were not significantly different. The authors conclude that there is no difference in the oxygen capacity of blood of infants born postmaturely as compared with that of term infants. No studies were made of the hemoglobin concentration or of the percentage of fetal and adult hemoglobin partition or of the oxygen content or tension of the umbilical vein blood.

Fetal Blood Studies: VII. The Oxygen Pressure Gradient Between the Maternal and Fetal Bloods of the Human in Normal and Abnormal Pregnancy.—Oxygen tensions were calculated from the oxygen-hemoglobin dissociation curve on blood obtained from intervillous space, umbilical artery, and umbilical vein nearly simultaneously in both normal and abnormal pregnancies. pH studies on these bloods were not performed. It is well known that alterations in the pH will change the position of the oxygen-hemoglobin dissociation curve and that significant errors in calculated tensions can be made when the pH is not known. Despite this objection, the studies reveal that in the normal pregnancy there is oxygen pressure difference of approximately 20 mm. of mercury, while in the abnormal pregnancy this is below 10 mm. of mercury. The reason for the reduction in tension in the abnormal pregnancy state is apparently decreased oxygen tension in the intervillous space, because there is little difference in the abnormal and normal fetal blood oxygen tensions.

Canadian Medical Association Journal, Montreal

77 (Oct. 1) 1957

The Changing Role of the Children's Hospital. M. J. E. Senn.—p. 647.
The Pediatricians of Red Lion Square. A. Ross.—p. 655.
° Kernicterus in Prematures. J. W. Gerrard.—p. 661.
Present Status of Poliomyelitis Vaccination. R. D. Defries.—p. 663.
° Attenuation of Chickenpox with Gamma Globulin. G. X. Trimble.—p. 697.

Kernicterus in Prematures.—The author discusses the etiology of kernicterus and its relation to the Rh and ABO factors. Hsia in 1952 showed that the incidence of kernicterus was closely related to the depth of jaundice in any baby. If the total serum bilirubin level remained below 20 mg. per 100 cc., kernicterus was rare. When the level rose to 30 mg. or more, half the babies developed this complication. Workers in Chicago and in Bristol, England, independently showed that neither Rh nor ABO incompatibility was essential to the disorder. It may depend on "the jaundice of prematurity, congenital spherocytosis, neonatal hepatitis and familial non-haemolytic jaundice."

Studies have shown that children may have an inborn error of metabolism and cannot convert indirect- to direct-reacting bilirubin. Six of eight cases whose indirect serum bilirubin level averaged a little above 20 mg. per 100 cc. developed kernicterus. There are, therefore, two overriding factors in the production of jaundice in the newborn: (1) hemolysis and (2) the temporary inability of the liver to convert indirect- into direct-reacting pigment.

Gerrard studied 91 cases of kernicterus associated for the most part with prematurity. None was due to hemolytic disease. Sixty-three infants died in the neonatal period, and the diagnosis was demonstrated at autopsy. Twenty-eight had survived the neonatal period and had varying degrees of choreoathetosis with or without deafness. Those weighing more than 2000 gm. at birth were likely to survive.

It takes about six days, on the average, in the absence of any hemolytic process to build up a dangerous level of bilirubin. This is in keeping with the observation that premature infants most commonly developed kernicterus on the sixth day of life. The only satisfactory way to prevent kernicterus in premature infants is by the removal of bilirubin by an exchange transfusion. The author therefore recommends a careful following up of serum bilirubin levels of premature babies from day to day and giving exchange transfusion to those whose levels appear to be rising above 18 mg. per 100 cc.

Attenuation of Chickenpox with Gamma Globulin.—Four cases of chickenpox in a hospital intern staff were observed over a period of three weeks. One intern died seven days after the onset of chickenpox. A second intern had a markedly febrile course for three days and a moderately severe rash but recovered. Two other persons who had been exposed but who were given γ-globulin, 1 cc. per 10 lb. of body weight, did have chickenpox, but it was mild, and they recovered without any difficulty.

Circulation, New York

16, No. 3 (Sept.) 1957

Aneurysmal Dilatation of the Aortic Sinuses in Marfan's Syndrome: Angiocardiographic and Cardiac Catheterization Studies in Identical Twins. I. Sternberg, J. Mangiardi, and W. Noble.—p. 368.
*Ventricular Septal Defects in the Infant Age Group. S. Zacharioudakis, K. Terplan, and E. Lambert.—p. 374.

16, No. 4 (Oct.) 1957

Truncus Anteriosus: Clinical Study of 14 Cases. Ray C. Anderson, William Obata, and C. Walton Lillehei.—p. 586.
Pathophysiology of Rheumatic Fever: Alterations in the Na^{24} Space and in the Exchangeable Sodium and Potassium Contents. Jerry K. Aikown.—p. 621.
Panel Discussion: Selection and Management of Patients for Cardiac Surgery. Howard B. Burchell, Moderator.—p. 631.

Ventricular Septal Defects in the Infant Age Group.—In the study 2586 consecutive autopies from 1936 to 1956 were reviewed, revealing 288 cases of major congenital heart disease. Twenty-three of these cardiac defects were found to be uncomplicated ventricular septal defects. These 23 cases were reviewed thoroughly. The age of the patients at death varied from 3 days to 15 months; 20 of 23 deaths occurred during the first 6 months of life.

The clinical symptoms and physical findings were similar to those presented in other reports of this condition. Failure to gain and recurrent episodes of respiratory infections were the chief complaints in all 23 cases.

Roentgenographic examinations, which were done in 17 cases, showed cardiac enlargement of moderate to marked degree in all. Increased hilar markings and convexity of the pulmonary segment were invariably present.

ECG's were taken in 15 patients; all of the tracings were abnormal; in 7, there was evidence of RVH; 2 graphs showed definite LVH; 6 of the tracings showed combined hypertrophy.

Cardiac catheterization was performed in six patients. All six patients showed an elevated systolic pressure in the right ventricle; these patients also had a rise in the blood oxygen content at the ventricular level exceeding 1 vol. %.

All of the 23 hearts examinated at autopsy were enlarged, showing dilatation and hypertrophy. This enlargement in 22 of the hearts involved the right heart primarily. Dilation of the pulmonary artery was a constant finding. Pulmonary congestion was an almost constant finding. The defects ranged in size from 3 to 19 mm. In 17 cases the defect was in the region of the outflow tracts posterior to the crista superventricularis and below the right and posterior aortic cusps. In this group two hearts had double openings; the second defect was found in the region of the inflow tracts under the posterior and septal leaflets of the tricuspid valve. In two cases the defects were located in the region of the outflow tracts anterior to the crista superventricularis just below the pulmonary valve. In the remaining two cases the defect involved the apical portion of the ventricular septum.

The authors concluded that their study had certain surgical implications. They felt that surgery had to be performed in the first few months of life if any significant decrease in the mortality rate of uncomplicated ventricular septal defects was to be achieved.

Journal of Pediatrics, St. Louis

51 No. 2 (Aug.) 1957

Hemodialysis in Children. F. H. Carter, S. Aoyama, R. D. Mercer, and W. J. Kolff.—p. 125.
The Social Management of the Epileptic Child and His Parents. S. Livingston—p. 137
Generalized Cytomegalic Inclusion Disease. A. E. McElfresh and J. B. Arey.—p. 146.
A Comparison of Intramuscular and Oral Benzathine Penicillin G in the Treatment of Streptococcal Infections in Children. B. B. Breese and F. A. Disney.—p. 157.
The Early Diagnosis of Patent Ductus Arteriosus. L. M. Holve and F. H. Adams.—p. 164.
Tetanus. D. Pinheiro.—p. 171.
Chlorpromazine in Pediatric Surgery. F. Tevetoglu and J. A. Abbey.—p. 181.
*Low Cerebrospinal Fluid Glucose Associated with Meningeal Neoplasia. W. T. Dungan and R. M. McKey.—p. 186.
Obstruction to Left Atrial Outflow by a Supravalvular Stenosing Ring. N. J. Johnson and K. Dodd.—p. 190.
Considerations on an Unrecognized Mediastinal Cyst. J. Storer and C. Kiragus.—p. 194.
Foreign Body (Paper Clip) in the Esophagus of a Young Infant. S. J. Nichamin and W. S. Gonne.—p. 197.
The Early Definitive Diagnosis of Patients with Congenital Heart Disease. F. H. Adams.—p. 202.
The Transacental Transmission of Poliomyelitis. P. Barsky and A. J. Beal.—p. 207.
Severe Infections in Splenectomized Infants and Children. R. J. Blattner.—p. 223.

51, No. 3 (Sept.) 1957

Congenital Sulfhemoglobinemia. A. A. Miller.—p. 233.
Paper Electrophoretic Study of Serum Proteins in Children with Leukemia. E. F. Gilbert, E. C. Rice, and K. O. Gregory.—p. 238.
Steroid Therapy for Rheumatic Fever. C. M. McCue.—p. 255.
Influence of l-Lysine Supplements on the Absorption and Retention of Nitrogen from Milk by Children with Protein Malnutrition. F. Gomez, R. Ramos-Galvan, J. Cravioto, S. Frank, C. de la Pena, M. E. Moreno, and M. E. Villa.—p. 262.
Studies on Protein Metabolism in Undernourished Infants and Children. N. S. Matsaniotis.—p. 267.
* The Management of Facial Trauma in Infants and Children. E. G. Stanley-Brown and R. B. Stark.—p. 285.
Niemann-Pick Disease in a Boy of 16 Months. B. Pansky and R. Lee.—p. 290.
Frequency of Cerebral Lateral Dominance Variations Among School Children of Premature and Full-Term Birth. T. H. Eames.—p. 300.
Congenital Leukemia Associated with Mongolism. C. H. Lee and E. Ciner.—p. 303.
Anhidrotic Ectodermal Dysplasia with Vascular Purpura. H. A. Pearson and T. E. Cone.—p. 306.
Constant Infusion Pump for Limiting Fluids. D. B. Strominger, D. H. James, and D. Goldring.—p. 310.
Child Care in Russia. H. Bakwin.—p. 313.

51, No. 4 (Oct.) 1957

Oropharyngeal Tularemia. W. T. Hughes and J. N. Etteldorf.—p. 363.
The Time of Passage of the First Stool and Urine by the Premature Infant. I. Kramer and S. N. Sherry.—p. 373.
Ectopic and Hypoplastic pituitary with Adrenal Hypoplasia. R. M. Ehrlich.—p. 377.
The Nephrotic Syndrome Associated with Renal Vein Thrombosis. B. Feinerman, E. C. Burke, and R. C. Bahn.—p. 385.
Septicemia of the Newborn Due to Listeria Monocytogenes. J. Wiener.—p. 392.
Urinary Calculus Disease Among Israeli Immigrant and Arab Children. D. Levy and W. Falk.—p. 404.
Proctalgia Fugax Infantum. C. M. Pounders.—p. 413.
Congenital Defect in the Musculature of the Stomach Resulting in Spontaneous Gastric Perforation in the Neonatal Period. J. L. Meyer.—p. 416.

Fatal Acute Appendicitis in a Fifteen-Day-Old Infant. J. H. Shinaberger, E. J. Tomsovic, and W. C. Butz.—p. 422.
Appendicitis in the Newborn Infant. R. H. Walker.—p. 429.
Unusual Auricular Flutter in Newborn Infant. L. E. Siderides, N. A. Antonius, and A. Richlan.—p. 435.
Favism. H. C. Tolmas.—p. 445.
Idiopathic Hypoproteinemia. T. J. Degnan.—p. 448.
Anomaly of the Inferior Vena Cava. W. M. Edwards and C. E. Bennett.—p. 453.
° Pulmonary Interstitial Emphysema with Air-Block Syndrome. E. J. Berman and A. J. Kahn.—p. 457.

Low Cerebrospinal Fluid Glucose Associated with Meningeal Neoplasia.—The authors refer to reports of low spinal fluid sugar associated with diffuse neoplastic involvement of the leptomeninges. They report a case of a 4-year-old child admitted because of intermittent headache, vomiting, and lethargy of six weeks' duration and strabismus and facial weakness of one day's duration. Physical examination revealed paralysis of the left abducens and partial peripheral right seventh nerves and slight motor weakness of the right leg. The spinal fluid sugar was 10 mg. per 100 cc., with a blood sugar of 62 mg. per 100 cc.; there were 11 cells, 4 polymorphonuclear cells and 7 lymphocytes. Two other spinal fluid sugar determinations during the next week were 18 and 15 mg. per 100 cc., with blood sugar of 87 and 74 mg. per 100 cc., respectively. The patient was found at autopsy to have many nodules of tumor scattered through the brain and generalized meningeal involvement by tumor cells. Diagnosis was a poorly differentiated glioma.

The mechanism of production of low spinal fluid sugar is unexplained in neoplastic meningitis. When present, it is a sign of diffuse meningeal involvement. A variety of neoplastic diseases may produce this, such as metastatic carcinoma, glioma, sarcoma, lymphoma, leukemia, and melanoma. The most likely incorrect diagnosis in children is tuberculous meningitis and possibly fungi involving the nervous system.

The Management of Facial Trauma in Infants and Children.—The authors were prompted to write this article because of the large number of infants and children they encountered who had improperly managed facial wounds. They point out that scar tissue developing from this improper treatment makes plastic revision very difficult and often unsatisfactory. This resulting disfiguration may cause long-lasting emotional disturbances in a patient.

Many of the wounds received are ragged and lacerated, and many are contaminated with cinders and dirt. The child is usually very frightened, and a very sympathetic, kind, and understanding approach by the physician is essential. After emergency treatment, such as stopping bleeding and ensuring an adequate airway, is carried out, one should take enough history to give one an idea as to whether multiple injuries are present, as well as looking for a history of epilepsy, blood dyscrasia, drug sensitivities, etc. A complete physical examination should be done.

The wound should be adequately examined to determine the extent of damage and the best method of repair. The authors state that deep and extensive laceration and especially wounds of any significance around the eyes and mouth should be repaired with use of general anesthesia, not local. Smaller wounds in cooperative patients may be handled by local anesthesia. A small incised, clean wound on a flat surface may be treated with a "butterfly" strip. Five fundamental concepts of wound healing must be adhered to: (1) thorough cleansing, (2) no foreign material (including strangulated tissue, large knots, and long suture ends), (3) absolute hemostasis, (4) exact approximation of all parts and obliteration of dead space, and (5) use of the finest suture material appropriate, usually 00000 or 000000 or 0000000. The authors go into detail about methods of cleaning the wound and suturing. They advise against shaving of eyebrows, for apparently they may not grow back if shaved.

In discussing animal bites, they advise against cauterization. They recommend cleansing and suturing; they do not allow them to heal from the bottom. Appropriate antibiotics, tetanus immunization, and antirabies treatment (antiserum and vaccination), if indicated, should be used.

The remainder of the article deals in some detail with various types of injuries about the face. They reiterate their plea for "more careful, scrupulous and considerate care of facial trauma in infants and children."

Pulmonary Interstitial Emphysema with Air-Block Syndrome.—The authors report a case in a newborn infant. The infant, delivered by section, was all right after birth but started developing respiratory difficulty at 18 hours of age. On physical examination moderate cyanosis was present; the chest expansion seemed limited, with sternal protrusion with

respiration; breath sounds were normal, but heart sounds were very indistinct; x-rays showed a shift of the mediastinum to right, atelectasis of the right upper lobe, and air in the anterior mediastinum. Thoracotomy plus surgical mediastinotomy apparently saved the baby's life.

The authors refer to an article by Macklin and Macklin which considers that pulmonic emphysema "results in interstitial emphysema when air leaks through the perivascular ring of alveoli." Once air is interstitial, it can dissect along the vascular sheaths into the mediastinum and can cause tension in the mediastinum. It causes trouble in two ways: (1) by blocking venous return (mean pressures in venae cavae, pulmonary veins, and auricles are zero or less) and (2) by producing pulmonic interstitial emphysema.

Autopsy reports have shown that, in some cases at least, the leaks were in dilated alveoli behind plugs of mucus and keratinized material in smaller bronchi and bronchioles, these latter being too small for surgical aspiration. Quick suction of mucus from nose and throat and avoidance of positive-pressure administration of oxygen, when possible, at birth may help prevent it. The authors suggest that if the child's condition is very serious, needle aspiration of the mediastinum or surgical mediastinotomy may be life saving.

Medizinische Klinik, Munich

52, No. 32 (Aug. 9) 1957

*Catheterization of the Trachea in the Newborn. E. Saling.—p. 1364.

52, No. 34 (Aug. 23) 1957

Spread of Radioactivity. K. Bechert.—p. 1432.
The Japanese Experience Concerning the Injuries Produced by Atom Bombs. K. Miyoshi.—p. 1438.
Conditions of Injuries Due to Radioactivity and the Possibilities of Treatment. J. Becker and T. Fliedner.—p. 1456.
Injuries Produced by Radioactivity and Possibilities of Their Treatment. H. Langendorff and R. Koch.—p. 1468.
Pathophysiology of the Injury Due to Radioactivity. H. Hobitz.—p. 1474.
Contribution to the Injury Due to Radioactivity. F. Kuhlman, M. Staemmler, and H. Kogel.—p. 1480.
The Problem of Gene Injury by Ionizing Rays. R. Kepp, and D. Hofmann.—p. 1484.
The Problem of Transferring Results of Genetic Effects of Radioactivity to Man. H. Luers.—p. 1488.

52, No. 35 (Aug. 30) 1957

*Nutrition and Allergy (with Special Reference to the Thyroid Gland as Potentiator of Allergy). Wilhelm Weitz.—p. 1511.
*Is It Permissible to Use Marine Fish in a Sodium Poor Diet? H. Wenderoth and J. G. Rausch-Stroomann.—p. 1540.

52, No. 36 (Sept. 6) 1957

*Urgent Neurosurgical Procedures in Infants and Young Children. W. Umbach.—p. 1569.

52, No. 37 (Sept. 13) 1957

The Modern Treatment of Strabismus. W. Ehrich.—p. 1634.

52, No. 42 (Oct.) 1957

*Report of a Case of Dysostosis Multiplex with Some Peculiarities: Pfaundler-Hurler Disease. L. Winkelmann.—p. 1831.
*Jacutin Intoxication in Childhood. W. Falk and R. Hinrichs.—p. 1837.

Catheterization of the Trachea in the Newborn.—Instruments and use of visual control of the introduction of a catheter into the trachea of newborn infants is described in detail, with a discussion of the advantages of the new method in comparison with the methods used before.

Nutrition and Allergy (with Special Reference to the Thyroid Gland as Potentiator of Allergy).—Abundant food rich in protein increases allergy. In certain allergic diseases and predispositions a diet poor in protein is recommended.

Is It Permissible to Use Marine Fish in a Sodium-Poor Diet?—The sodium content of the fresh meat of some fish of the North Atlantic and the Baltic Sea was determined by means of the flame photometer. Such fish can be used in sodium-poor diets like meat, poultry, and fresh-water fish.

Urgent Neurosurgical Procedures in Infants and Young Children.—A short discussion is given of the indications for and the surgical relief of various neurological conditions in

infants and young children, such as meningocele, usually as encephalo- or myelomeningocele, including "Lückenschädel." Various forms of hydrocephalus, chronic intradural hematoma (pachymeningitis hemorrhagica interna), oxycephaly, and tumors. Certain types of cerebral infantile paralysis and porencephalic cysts are considered, as well as accidental trauma of the head, with consequent hematoma. Here an immediate examination by means of bur holes is recommended.

Report of a Case of Dysostosis Multiplex with Some Peculiarities: Pfaundler-Hurler Disease.—A girl 8 years of age presented the picture of typical dysostosis multiplex (Pfaundler-Hurler disease). Furthermore, the double glucose-tolerance test of Staub-Traugott was abnormal, and in the urine chromatogram a pentose spot was outlined.

Jacutin Intoxication in Childhood.—Jacutin is an insecticide consisting of γ-hexachlorcyclohexane in fumigation tablets. Within four years seven children took such tablets. The amount taken was calculated to vary from 50 to 120 per kilogram. The first symptoms were noted as early as about 10 minutes after ingestion in the children who took the highest dosage. In none were they delayed beyond one hour. With one exception all vomited. Epileptiform convulsions lasting from 30 minutes to 3 hours occurred, but neither tongue biting nor involuntary urination or defecation was noted. Following the convulsions, 6 to 10 hours after cessation of the status epilepticus, complete recovery had taken place. One of the children had an elevation of the blood sugar three and one-half hours after ingestion to 316 mg/100 ml. Guinea pigs which had been given Jacutin also responded with elevation of the blood sugar. Jacutin is hardly soluble in water but readily soluble in some organic solvents, and it is highly lipid-soluble. Therefore, milk should not be given. Gavage should be carried out and only saline laxatives should be used. To counteract the convulsions, intravenous administration of Epivan sodium or thiopental (Pentothal) is recommended.

New England Journal of Medicine, Boston

257, No. 4 (July 25) 1957

Tuberculosis in BCG-Vaccinated Nurses: A Report of Five Years' Experience at the Boston City Hospital. A. I. DeFriez and T. L. Badger.—p. 161.

* Reading Epilepsy. H. Stevens.—p. 165.

Complications from the Use of Tranquilizing Drugs. L. E. Hollister.—p. 170.

Brief Recording: A Clinical Comment on Postmaturity. C. L. Buxton.—p. 181.

257, No. 5 (Aug. 1) 1957

* Resection of Pulmonary Lesions Associated with Cystic Fibrosis of the Pancreas. L. L. Kulczycki, J. M. Craig, and H. Shwachman.—p. 203.

Suppuration and Calcification of the Liver and Spleen Due to Long Standing Infection with Brucella Suis. W. W. Spink.—p. 209.

Gastrointestinal Hemorrhage in Uremia: Report of Two Cases of Massive Hemorrhage Resulting from Causes Other than Uremic Enterocolitis. R. Scalettar, M. E. Rubini, and W. H. Meroney.—p. 211.

Sodium Diuresis from Amphenone Given to Patients with Cirrhosis and Ascites. S. J. Wolfe, B. Fast, J. M. Stormont, and C. S. Davidson.—p. 215.

Medical Problems in Lebanon. M. H. Shamma'a.—p. 218.

Melanin Pigmentation and Its Endocrine Control. S. Deutsch and H. Mescon.—p. 222.

Effect of Varying Doses of Reserpine on Gastric Secretion. D. Liebowitz and J. V. Carbone.—p. 227.

Isolation of Brucella Abortus by Percutaneous Liver Biopsy. F. B. Cohen, B. Robins, and W. Lipstein.—p. 228.

Hemopericardium with Cardiac Tamponade in Chronic Uremia. W. R. Guild, G. Bray, and J. P. Merrill.—p. 230.

Doctors Afield: Tobias Smollett and Dr. Antoine Fizes (A Medical Consultation in 1763). H. G. Brugsch.—p. 232.

257 No. 6 (Aug. 8) 1957

*Acute Benign Pericarditis Associated with Coxsackie Virus Group B, Type 5. S. B. Weinstein.—p. 265.

Melanin Pigmentation and Its Endocrine Control. S. Deutsch and H. Mescon.—p. 268.

Serum and Cerebrospinal-Fluid Transaminase Concentrations in Various Neurologic Disorders. R. M. Myerson, J. K. Hurwitz, and T. Sall.—p. 273.

Hepatic Dysfunction During Promazine Therapy. L. Waitzkin.—p. 276.

Current Concepts in Therapy: Analgesic Drugs; IV. Non-Narcotics; III. Clinical Use of the Salicylates.—p. 278.

257, No. 8 (Aug. 22) 1957

Epidemic Neuromyasthenia: An Outbreak of Poliomyelitislike Illness in Student Nurses. A. Shelokov, K. Habel, E. Verder, and W. Welsh.—p. 345.

Epidemic Neuromyasthenia: An Outbreak in Punta Gorda, Florida. D. C. Poskanzer, D. A. Henderson, E. C. Kunkle, S. S. Kalter, W. B. Clement, and J. O. Bond.—p. 356.

New Technic for Detection of Bacterial Contamination in a Blood Bank Using Plastic Equipment. C. W. Walter, R. B. Kundsin, and L. N. Button.—p. 364.

257, No. 9 (Aug. 29) 1957

A Controlled Study of Three Methods of Prophylaxis Against Streptococcal Infection in a Population of Rheumatic Children: I. Streptococcal Infections and Recurrences of Acute Rheumatic Fever in the First Two Years of the Study. H. F. Wood, G. H. Stollerman, A. R. Feinstein, I. Hirschfeld, J. H. Rusoff, A. Taranta, R. C. Haas, and J. A. Epstein.—p. 394.

Renal Tubular Acidosis with Recurrent Nephrolithiasis and Nephrocalcinosis. D. L. Wilansky and C. Schneiderman.—p. 399.

*Salmonella Osteomyelitis in Patients with Sickle-Cell Anemia. E. W. Hook, C. G. Campbell, H. S. Weens, and G. R. Cooper.—p. 403.

257, No. 10 (Sept. 5) 1957

Effects of Oral and Intramuscular Administration of Reserpine in Thyrotoxicosis. J. J. Canary, M. Schaaf, B. J. Duffy, and L. H. Kyle.—p. 435.

* Fatal Reactions to Penicillin: Evaluation of a Test for Sensitivity. V. M. Smith.—p. 447.

Clinical Applications of Radioactive Isotopes. J. D. Reeves.—p. 454.

A Case of Chicken-Pox Pneumonia with X-Ray Findings Suggesting Metastatic Carcinoma. H. G. Levin.—p. 461.

Ruptured Gastric Ulcer in an Eleven-Year-Old Boy. C. Bransmer, J. R. Fox, and E. R. Clarke.—p. 463.

257, No. 11 (Sept. 12) 1957

Antibiotic Combinations: Tetracycline, Erythromycin, Oleandomycin and Spiramycin, and Combinations of Tetracycline with Each of the Other Three Agents; Comparisons of Activity in Vitro and Antibacterial Action of Blood After Oral Administration. W. F. Jones Jr. and M. Finland.—p. 481.

Intravenous Infusion of Bone Marrow in Patients Receiving Radiation and Chemotherapy. E. D. Thomas, H. L. Lochte Jr., W. C. Lu, and J. W. Ferrebee.—p. 491.

* Clinical and Laboratory Studies of Mumps: I. Laboratory Diagnosis by Tissue-Culture Technics. J. P. Utz, J. A. Kasel, H. G. Cramblett, C. F. Szwed, and R. H. Parrott.—p. 497.

Femoral Arteriography: A Simple and Safe Method. D. C. Nabseth and M. Ritvo.—p. 502.

Disaster in Pedagogy. R. A. Lyman Jr.—p. 504.

Clinical Applications of Radioactive Isotopes. J. D. Reeves.—p. 507.

The Shape of Things to Come: A Guide to the Newer Medical Education. P. J. White.—p. 513.

Current Concepts in Therapy.—p. 513.

Erythromycin, Oleandomycin and Spiramycin and Their Combinations with Tetracycline.—p. 525.

257, No. 12 (Sept. 19) 1957

Hypoaldosteronism: A Clinical Study of a Patient with an Isolated Adrenal Mineralocorticoid Deficiency, Resulting in Hyperkaliemia and Stokes-Adams Attacks. J. B. Hudson, A. V. Chobanian, and A. S. Relman.—p. 529.

Antibiotic Combinations: Tetracycline, Erythromycin, Oleandomycin and Spiramycin and Combinations of Tetracycline with Each of the Other Three Agents; Comparisons of Activity in Vitro and Antibacterial Acion of Blood after Oral Administration. W. F. Jones and M. Finland.—p. 536.

*The Clinical Significance of Serum Transaminase in Infectious Mononucleosis Complicated by Hepatitis. L. E. Rennie and F. Wroblewski.—p. 547.

Coexistence of Intussusception and Henoch's Purpura. I. D. Steinhardt and A. F. Jonas.—p. 553.

The Atomic Age and Radiology. F. W. O'Brien.——p. 556.

Clinical Applications of Radioactive Isotopes. J. D. Reeves.—p. 559.

Cross-Sensitization of the Feet and Hands Due to Chrome-Tanned Leather Shoes and Gloves. G. E. Morris.—p. 567.

257, No. 13 (Sept. 26) 1957

Neurologic Manifestations of Chronic Pulmonary Insufficiency. F. K. Austen, M. W. Carmichael, and R. D. Adams.—p. 579.

Infectious Hepatitis: Report of an Outbreak Probably Caused by Drinking Water. J. W. Mosley and W. W. Smither.—p. 590.

* Severe Nonfatal Histoplasmosis: Report of a Typical Case, with Comments on Therapy. Harry Rubin et al.—p. 599.

The Triad of Medicine: Education, Practice and Research. N. Y. Wessell.—p. 603.

Clinical Applications of Radioactive Isotopes. J. D. Reeves.—p. 605.

257, No. 14 (Oct. 3) 1957

Erythroblastosis Fetalis. F. H. Allen and L. K. Diamond.—p. 659.

257, No. 15 (Oct. 10) 1957

Acute Pancreatic Lesions in Patients Treated with ACTH and Adrenal Corticoids. F. A. Carone and A. A. Liebow.—p. 690.

Equine Encephalitis in Massachusetts. R. F. Feemster.—p. 701.

Erythroblastosis Fetalis. F. H. Allen and L. K. Diamond.—p. 705.

Double Tracheoesophageal Fistula Without Atresia: Report of a Case. D. P. Babbitt.—p. 713.

Current Concepts in Therapy.—p. 715.

257, No. 16 (Oct. 17) 1957

Management of the Circulatory, Inflammatory and Metabolic Complications of Mitral Valvulotomy. A. V. N. Goodyer and W. W. L. Glenn.—p. 735.

*Antibiotic Combinations: Antistreptococcal and Antistaphylococcal Activity of Normal Subjects After Ingestion of Erythromycin or Chloramphenicol or Both. W. F. Jones and M. Finland.—p. 744.

Care of Female Psychiatric Patients, Including the Acutely Disturbed, on an Open Medical and Surgical Ward. P. Castelnuovo-Tedesco.—p. 748.

Accumulation of Radioactive Iodine: Observations on Its Early Phase in Hyperthyroid, Euthyroid and Hypothyroid Subjects. W. P. Vanderlaan.—p. 752.

Radiation Hazards: I. Radiation Hazards in Medical Practice. O. S. Peterson.—p. 756.

Erythroblastosis Fetalis. F. H. Allen and L. K. Diamond.—p. 761.

Evaluation of Blood Cultures After Sigmoidoscopy. D. Unterman, M. B. Milberg, and M. Kranis.—p. 773.

End of the Mean (After the Manner of Oliver Wendel Holmes Sr.). P. J. White.—p. 775.

Reading Epilepsy.—The authors report cases of a rather newly delineated syndrome, "reading epilepsy." They point out that in dealing with epilepsy one must take a thorough history of the "premonitory and sequential pattern of events that introduce the seizure." This may reveal the epileptogenic focus and permit precise classification of the disorder.

Reading epilepsy may be one of two types—primary or secondary. In secondary reading epilepsy seizures may occur spontaneously or may be precipitated by stimuli other than reading, especially photic. The jaw-jerking phenomenon is absent, and the electroencephalogram is often abnormal.

The case is that of a 24-year-old woman who had had three convulsions, all associated with reading and preceded by jaw-jerking, with repetitive single twitches. Four electroencephalograms during sleep and waking were normal. However, when she started to read Hebrew, a difficult subject, "a crescendo of spike discharges was precipitated, eventuating in jaw-twitching followed by a feeling of warmth and then of being dazed." With Dilantin therapy and less reading she had no more seizures, although the jaw-jerking continued on reading.

The authors reported two cases of secondary reading epilepsy in boys, one 11 years old and one 17 years old. Other stimuli besides reading could precipitate their attacks.

The authors point out that reading familiar prose or music did not cause trouble but that reading a language or subject that called for more concentration led to the phenomenon of reading epilepsy.

Resection of Pulmonary Lesions Associated with Cystic Fibrosis of the Pancreas.—The authors point out that the pulmonary manifestations in cystic fibrosis of the pancreas are the most important and serious aspect of the disease. Furthermore, though the largest number of patients have a combination of intestinal and pulmonary symptoms by the age of one year, still a significant number are discovered in older age groups, in which the common complaints are bronchiectasis, recurring pneumonia, and asthma, with few or no intestinal symptoms. Over 90% of patients have pulmonary involvement by x-ray at the time the diagnosis is made. Irregular aeration and lobular patches of atelectasis, with widespread superimposed infection, suggest cystic fibrosis of the pancreas. Lobar or segmental atelectasis is apt to occur in small infants and persist for months. It is said to be a bad prognostic sign.

The authors report on six children in whom lobectomies were performed, in two of them before the diagnosis was made. Four of the six children are doing well from one to eight years later. Two others were improved. The two youngest patients had lobectomy at 16 months and 22 months became of persistent atelectasis which would not clear on medical management. All these patients had minimal disease elsewhere in the lungs. They have received the usual regimen of antibiotics, vitamins, pancreatin, expectorants, aerosols, and postural drainage. The authors did not believe that any of the other patients (more than 600) they saw with cystic fibrosis of the pancreas would be helped by operation, because of the widespread involvement of the lungs. They conclude that in the occasional, well-selected patient with cystic fibrosis of the pancreas lobectomy or segmental resection of the lung involved may be of very definite benefit.

Acute Benign Pericarditis Associated with Coxsackie Virus Group B, Type 5.—The author reports the case of a 25-year-old man who became ill with chest pain, aggravated by respiration, fever, and shortness of breath on reclining. Over a six-week period he would get better and worse. The pain radiated to back and left shoulder. When he was admitted to the hospital physical examination was essentially negative. The sedimentation rate was elevated; chest x-ray revealed an enlarged cardiac silhouette, and an ECG demonstrated inverted

T-waves in Lead aV_F and all precordial leads, compatible with pericarditis or myocarditis. Complement-fixation titers to Coxsackie B, Type 5 virus were 1:512 on admission, 1:256 one week later, and 1:16 five months later. The patient was discharged from the hospital on the fifth day and has remained well.

The disease, acute benign pericarditis, is not too uncommon. Etiology has not been uniformly determined, although pericarditis has been reported in atypical pneumonia, lymphogranuloma venereum, infectious mononucleosis, and Bornholm disease (thought to be due to Coxsackie virus). Myocarditis, due to Coxsackie virus, Group B, Types 3 and 4, has been reported in infants. The author feels that, though the virus was not isolated, the drop in titer to Coxsackie virus, Group B, Type 5, which occurred after the disease, is good evidence that Coxsackie virus, Group B, must be considered as a cause of acute benign pericarditis.

Salmonella Osteomyelitis in Patients with Sickle-Cell Anemia.—The authors review the literature on Salmonella infections in patients with sickle-cell anemia and add four cases of their own. One was 15 months; one, 3 years; one, 22 years, and one, 23 years of age. One patient had a bacteremia only; the other three had osteomyelitis, one of whom had multiple bones involved.

The authors were able to find 33 cases in the literature, of which 31 had osteomyelitis and 2 had bacteremia with Salmonella. There were three times as many males involved as females. S. typhimurium and S. paratyphi B accounted for 67% of the cases. Two-thirds of the patients showed multiple bone lesions. The difficulty, both by symptoms and by x-ray, of differentiating between osteomyelitis and the bone pain and aseptic necrosis which occurs in sickle-cell anemia was discussed. Diagnosis usually made by aspiration of pus or from blood culture. It was also pointed out that, though the organisms were usually sensitive to chloramphenicol, the lesions were not usually sterilized and may become active again even after a period of years.

Possible causes suggested were that (1) capillary thrombosis in the gastrointestinal tract may make it less capable of resisting invasion by intestinal organisms (a somewhat analogous situation occurs following gastrectomy and gastroenterostomy); (2) debility and the autosplenectomy that occurs may predispose to infection; (3) areas of ischemia and necrosis which often occur in the bones in patients with sickle-cell anemia may allow for the growth of the bacterium at that point; the ischemia of bone marrow, which may be present, may reactivate an old lesion.

The authors feel that there is a definite relationship between sickle-cell anemia and Salmonella osteomyelitis.

Fatal Reaction to Penicillin: Evaluation of a Test for Sensitivity.—The author states that about 1000 deaths, at least, have resulted from immediate anaphylactic reactions to penicillin in the United States alone and points out that many times the penicillin was given for other than life-saving purposes in the physician's office. The author also states that the usual testing for penicillin sensitivity requires special dilutions, special handling, etc., and is often either not available or too time-consuming. In order to try to find a safe and yet easy way to predict sensitivity of the immediate, anaphylactic type, the author studied the following procedure: 1. A scratch (about 4 mm. long) was made on patient's forearm with a hypodermic needle (without drawing blood), and a drop of procaine penicillin, 300,000 units per milliliter, was applied. 2. A drop of same solution was placed on the lower eyelid; both sites were watched for 20 minutes; itching, redness, or edema of the eye within 20 minutes was a positive reaction; areas of erythema of skin of 1.0 cm. or less were noted in 99% of those tested; positive skin test was defined as an area of erythema more than 1 cm. in diameter or a wheal, or both, within 20 minutes.

Of the 1365 patients tested, 64 had a history of previous sensitivity (48, delayed urticaria; 4, serum-sickness type, and 12, anaphylactic collapse within minutes of a penicillin injection). Of the 1365 patients, only one had a systemic reaction to the test, and this was easily controlled by epinephrine. Of 798 patients (army personnel) who were sent in for penicillin shots, 20 had positive tests and were not given penicillin. Of the remaining 778, one patient had a mild anaphylactic reaction a few minutes after receiving penicillin in spite of a negative test. It was easily controlled by epinephrine. One patient who had a positive eye test (but negative skin test) went to a private physician a week later and was given penicillin. He died five minutes later with an anaphylactic reaction. Seven other patients with a history of a recent anaphylactic reaction were tested by this method, and all were found to have positive reactions to both skin and eye tests. Of 12 patients with histories of anaphylactic reactions, 10 had positive tests and

2 had negative tests; the positives had had recent reactions, whereas the negatives had had reactions 18 and 39 months previously. No correlation was noted between immediate test responses and delayed penicillin reaction (such as serum sickness and urticaria).

The author feels that this test is simple, without real danger, and very useful to pick out those patients who might have an immediate anaphylactic reaction.

Clinical and Laboratory Studies of Mumps: I. Laboratory Diagnosis by Tissue-Culture Technics.—The authors discuss the present status of the diagnosis of mumps by present laboratory methods, pointing out that antibody studies or isolation by inoculation of embryonated hens' eggs takes time; therefore at present the diagnosis of mumps is usually made at a time when the patient has recovered.

The authors discovered that inoculating monkey kidney tissue cells and HeLa cells with mumps virus produced a characteristic cytopathogenic effect, different from that produced by other viruses. By neutralization and other tests they identified the virus as that of mumps. The effects were noticed from three to six days after inoculation. Also, by tissue culture neutralization tests with antimumps guinea-pig serum the diagnosis can be practically confirmed fairly early.

A total of 21 patients with clinically characteristic mumps were studied; 42 specimens from these patients yielded cytopathogenic agents; 32 agents from these 42 specimens were studied, and all were proved to be mumps virus. Virus was recovered from saliva and swabs of Stensen's ducts from the 2d to the 8th day of illness; from urine from the 2d to the 13th day of illness; in two patients with meningoencephalitis virus was recovered from the spinal fluid. A total of 76% of the specimens from the mouth were positive in the first five days of the illness.

The authors conclude that there is little doubt that they have isolated mumps virus in tissue culture, and they feel that this method enables them to make a definite diagnosis earlier than other methods allow.

The Clinical Significance of Serum Transaminase in Infectious Mononucleosis Complicated by Hepatitis.—The authors refer to the fact that hepatitis, icteric or nonicteric, usually complicates infectious mononucleosis. They feel that the usual tests for liver function are positive but do not reflect the clinical course. Since SGP-T (serum glutamic pyruvic transaminase) and SGO-T (serum glutamic oxaloacetic transaminase) seem to be more sensitive indications of liver damage in patients with hepatitis, the authors set up this study of 32 patients to determine if measuring transaminase levels was a better index of the course of hepatitis in infectious mononucleosis.

Of the 32 patients, all but 1 had an elevated SGP-T value and 5 had normal SGO-T. In general, a reversion of SGP-T levels toward normal coincided with diminution of subjective symptoms. Neither steroids nor antibiotics changed the course. Relationships between other liver-function tests noted were as follows: 1. Abnormal sulfobromophthalein (Bromsulphalein) retention appeared when SGP-T reached 125 units or more. 2. Serum total bilirubin increased when SGP-T reached 375 units or more. 3. Abnormal cephalin-flocculation occurred when SGP-T revealed 60 units or greater. 4. Abnormal thymol turbidity occurred when SGP-T reached 100 units or more. In other febrile illnesses and diseases involving the lymphatic and/or hematopoietic systems without liver disease, SGP-T and SGO-T tended to be normal.

The authors feel that it is of some importance to detect hepatic involvement, because there is evidence that nonicteric hepatitis of various causes may be a cause of cirrhosis of the liver. Furthermore, the finding of abnormal levels of transaminase may be a help in detecting, following, and treating patients with infectious mononucleosis.

Severe Nonfatal Histoplasmosis: Report of a Typical Case, with Comments on Therapy.—The author reports a case of nonfatal severe histoplasmosis, which he feels is a common form of the disease. The onset was with fever and severe, shaking chills. Apparent source of the infection was a chicken coop which the patient cleaned out. Physical examination was essentially negative. Laboratory studies revealed a WBC count of 14,000, with a predominance of neutrophils. Urine showed a trace of albumin. Histoplasmin and blastomycin skin tests were positive. X-ray of chest revealed diffuse small mottled areas of infiltration throughout both lung fields. During the hospital stay the major symptoms were fever, shaking chills, and prostration. Only slight cough occurred. Evidence of vitamin deficiency developed, probably from the marked metabolic demands made by the disease. On the 11th day a maculopapular erythematous rash was noted on the trunk and upper extremities which became confluent over the entire body.

Laboratory diagnosis was based on a positive culture from gastric washings and positive serologic tests. Complement-fixing antibodies and precipitins developed to the histoplasmin phase by the 23d day, after being negative on the 14th day (after exposure). Three weeks later they were negative. The precipitin test, especially, shows a rapid rise and fall; the complement-fixation test may persist for several months; tests against the yeast phase were negative, which is not unusual. In this case the return of serological tests to normal was faster than usual; possibly this was related to the treatment. Treatment was with a new antibiotic with antifungal properties, Amphotericin B. It was given in doses of 1.2 gm. every three hours by mouth with little effect. When it was given daily in a dose of 50 mg. in 500 ml. of 5% dextrose over a six-hour period, the temperature started to go down. The authors believed that this suggested an effect on the disease, although they recognized that this pulmonary form of the disease, without apparent involvement of other organs, is rarely fatal. Another point in favor of a possible effect of the drug was the rapid clearing of pulmonary infiltrates. The authors felt that this commoner form of the disease and some of its clinical and laboratory features, together with the possible beneficial effect of Amphotericin B, should be brought to the attention of the medical profession.

Antibiotic Combinations: Antistreptococcal and Antistaphylococcal Activity of Normal Subjects After Ingestion of Erythromycin or Chloramphenicol or Both.—This article is another one of a series by these authors dealing with combinations of antibiotics. The ones compared here are erythromycin in single doses of 500 and 1000 mg., chloramphenicol in single doses of 500 and 1000 mg., and combinations of the two in doses of 250 mg. of each and 500 mg. of each. The importance of these two drugs has been highlighted lately because of the increased incidence of staphylococcal infections, resistant to most other drugs.

The method of testing was to give six normal young men, in random rotation, the dosage of drug. Each volunteer received each different dose and combination at the three-day intervals. Plasma samples were taken before ingestion of the drug and at 1, 2, 5, 8, 12, 16, and 24 hours afterward. Their specimens were tested for activity against Streptococcus 98, Staphylococcus 209P, and Staphylococcus 400. The authors state that there was remarkable uniformity in the results of the tests done at different times.

Results with Streptococcus 98 showed that the greatest activity was shown by the 1000 mg. dose of erythromycin; next was the 500 mg. dose of erythromycin; then, the combination of the two with 500 mg. of each; then, the combination with 250 mg. of each. Chloramphenicol in a dose of 1000 mg. was next; the 500 mg. dose of chloramphenicol gave only a slight and transient effect.

Results with the two staphylococci (one of which was highly susceptible to penicillin and one of which was highly resistant) paralleled those to the Streptococcus except that they were lower. The 500 mg. dose of chloramphenicol gave no detectable activity. The finding that the combination of 500 mg. of each drug showed slightly lower activity than 500 mg. of erythromycin alone suggested, perhaps, very slight antagonism. This was, of course, entirely in vitro work. The authors further point out that in vitro experiments have shown that (1) staphylococci rapidly develop resistance to erythromycin and (2) chloramphenicol has a rather marked effect on delaying this development of resistance to erythromycin. They feel this is probably true in vivo also.

News and Comment

ANNOUNCEMENTS

Postgraduate Courses at Harvard Medical School.—The Harvard Medical School announces two postgraduate courses. General pediatrics will be covered from June 2 to June 9, inclusive, and pediatric metabolism and endocrinology, from June 10 to June 13, inclusive. Enrollment may be for the entire course or for the last four days. These courses are to be held at the Burnham Memorial for Children of the Massachusetts General Hospital and are under the direction of Dr. Allan M. Butler and Dr. Nathan B. Talbot. For information write to Assistant Dean, Courses for Graduates, Harvard Medical School, Boston 15.

Residency in Pediatric Oncology at Memorial Hospital.—Applications for the residency from Jan. 1, 1959, to Dec. 31, 1959, in Pediatric Oncology at Memorial Center for Cancer and Allied Diseases in New York will be received up to July 1, 1958. This residency is approved for partial credit by the American Board of Pediatrics and is limited to the neoplastic diseases of children. Salary is $4300 annually plus maintenance. For application forms and information write to Director, Pediatric Service, Memorial Center for Cancer and Allied Diseases, 444 E. 68th St., New York 21.

Seventh Annual Postgraduate Seminar for Pediatricians.—The Seventh Annual Postgraduate Seminar for Pediatricians will be held at St. Christopher's Hospital for Children, Philadelphia, on Wednesday, May 21, 1958, at 10 a. m., through Saturday, May 24, noon. The seminar faculty will include staff members of Temple University School of Medicine, St. Christopher's Hospital for Children, and Temple University Hospital. The course will consider endocrine, hematologic, cardiac, and neurologic disorders; staphylococcal infections; problems of pediatric surgery; conditions of the newborn infant, and other pediatric subjects.

A Seminar tradition, the Saturday morning session provides an opportunity to ask questions of the entire Seminar staff gathered as a panel. Specific cases or problems from practice can also be discussed with staff members in personal conferences.

Mail registration to Dr. John B. Bartram, St. Christopher's Hospital for Children, Philadelphia 33. The fee, including one seminar dinner ticket and all lunches is $75. Write for further information about hotels or for help on reservations.

Refresher Course.—The Children's Hospital of Philadelphia and the Graduate and Undergraduate Schools of Medicine, University of Pennsylvania, announce a series of short refresher courses in 1958 for practitioners, pediatricians, and clinical pathologists, to be held in the auditorium of the hospital, 9:00 a. m. to 5:00 p. m., 1740 Bainbridge St., Philadelphia 46.

All courses will emphasize developments of the past few years which are important to the physician in practice. There will be panel discussions, demonstrations, conferences, and case presentations.

1. *Pediatric Advances.*—Monday through Friday, May 26 through 30, 1958. Conducted by the staff of The Children's Hospital of Philadelphia, in collaboration with the Department of Pediatrics of the University of Pennsylvania.

The curriculum will consist of a series of clinics, conferences, and panel discussions in selected aspects of contemporary pediatrics in which important advances are being made: allergy, cardiology, endocrinology, erythroblastosis fetalis, fluid and electrolyte balance, gastroenterology, hematology, infectious diseases, kidney diseases, neurology, neurosurgery, orthopedics, retardation, roentgenology, therapy, and pediatric surgery.

This course has been given Category I accreditation by the American Academy of General Practice.

Tuition: $115.00, payable with the application.

2. *Practical Pediatric Hematology.*—Monday, Tuesday, and Wednesday, June 2, 3, and 4, 1958. Conducted by Irving J. Wolman, M.D., and other members of the hematology department.

The topics will include function, normal ranges, and disturbances of hemoglobin, erythrocytes, leukocytes, and platelets as related to age and prematurity; performance and interpretation of the bone marrow examination; the various childhood anemias and approaches to their investigation; splenomegaly and related disturbances; the hemorrhagic diseases, including the sub-

varieties of hemophilia; diagnosis and management of leukemia and the lymphomatous diseases; advances in blood grouping and in transfusion therapy.

Tuition: $75.00, payable with the application.

An illustrative collection of 25 abnormal blood and bone marrow slides has been prepared. These are available for purchase: $10.00 for registrants; $15.00 for nonregistrants.

3. *Hemolytic Disease of the Newborn.*—Thursday and Friday, June 5, and 6, 1958. Conducted by Thomas R. Boggs Jr., M.D., and Milton C. Westphal, M.D., of the Philadelphia Serum Exchange of The Children's Hospital of Philadelphia.

The topics will include Rh and other blood groups; diagnosis and management of the erythroblastotic infant; demonstrations of laboratory procedures; exchange transfusion.

Tuition: $50.00, payable with the application.

Applications and correspondence should be forwarded to Irving J. Wolman, M.D., Children's Hospital of Philadelphia, 1740 Bainbridge St., Philadelphia 46.

Summer Clinic in Denver.—The Tenth Annual Summer Clinics of The Children's Hospital, in Denver, will be held June 18, 19, and 20, 1958. Designed for all physicians concerned with the care of infants and children, the course will present recent advances in medical knowledge appropriate to practice and will emphasize early recognition of disease and common problems in the management of children's diseases and will outline successful programs of therapy.

Guest faculty this year will be Dr. Lee Forrest Hill, Chief of Staff, Raymond Blank Memorial Hospital, Des Moines, and Past President, American Academy of Pediatrics; Dr. Meyer A. Perlstein, Professor of Pediatrics, Cook County Hospital, Chicago, and member of Medical Advisory Board of the National Society for Crippled Children, and Dr. William B. Kiesewetter, Associate Professor of Surgery, University of Pittsburgh School of Medicine, Surgeon in Chief, Children's Hospital of Pittsburgh.

Further information can be secured by writing the Chairman, Summer Clinics Committee, Children's Hospital, Denver 18.

GENERAL NEWS

Handbooks on Fluoridation Available for Community Use.—To aid in community education on water fluoridation, the Committee to Protect Our Children's Teeth, citizens' group headed by Dr. Benjamin Spock, is making available two handbooks.

"Our Children's Teeth" is a 104-page digest of expert opinions on various aspects of fluoridation, designed to serve as a handy basic reference source. Authors include Drs. Herman E. Hilleboe, New York State Health Commissioner; H. Trendley Dean, Secretary, Council on Dental Research, American Dental Association; Thomas Parran, Dean, Graduate School of Public Health, University of Pittsburgh, and former Surgeon General, U. S. Public Health Service; Robert A. Kehoe, Director, Kettering Laboratory; Reidar F. Sognnaes, Professor of Oral Pathology, Harvard University, and Detlev W. Bronk, President, National Academy of Sciences.

The volume includes a statement by leading American authorities on human nutrition, an explanation of the chemistry of fluorine by the nation's foremost chemists, a chronology of the fluoridation movement, summary of experience in major cities, a statement on the legality of fluoridation, and a roster of national organizations supporting the measure.

"Gains and Setbacks" is a digest of experiences in more than thirty communities, designed as a guide in the planning of a public education campaign. It includes articles by public health authorities and experts in mass communications as well as a U. S. Public Health Service report on the status of fluoridation throughout the country, a summary of court action on the measure, and a comprehensive directory of source material.

Both books may be orderd from the Committee to Protect Our Children's Teeth, 105 E. 22d St., New York 10. "Our Children's Teeth" is priced at $1.00; "Gains and Setbacks" is priced at $1.50.

American Academy for Cerebral Palsy.—The American Academy for Cerebral Palsy held its 11th Annual Meeting in New Orleans (Headquarters at the Roosevelt Hotel) Nov. 24, 25, 26, and 27, 1957.

The officers for the forthcoming year are as follows: William T. Green, M.D., President, 300 Longwood Ave., Boston 15; Robert A. Knight, M.D., President-Elect, 869 Madison Ave., Memphis 3; Samuel B. Thompson, M.D., Treasurer, 930 Donaghey Bldg., Little Rock, Ark.; Raymond R. Rembolt, M.D., Secretary, University Hospital-School, Iowa City.

The 1958 Annual Meeting will be held in Providence, R. I., Sept. 25, 26, and 27, at the Sheraton Biltmore Hotel.

National Foundation for Infantile Paralysis.—Portions of a news release from the National Foundation for Infantile Paralysis are as follows:

"Though 1957 was marked by a tremendous campaign, sponsored by the National Foundation and the American Medical Association, to vaccinate the American public against paralytic polio," said Mr. O'Connor, "a shocking number of U. S. citizens are still unprotected.

"Only three out of five Americans in the susceptible age group under 40 have had one or more injections of Salk vaccine, according to revised Public Health Service estimates as of Dec. 1."

Public Health Service estimates on Dec. 1, 1957, listed 5,000,000 persons under 40 with only one Salk injection, 25,000,000 with two injections and 34,000,000 with all three injections. The total number of persons with one or more injections was estimated at 64,000,000 at the end of November. Some 45,000,000 have had none.

Children under 20 have the best vaccination record, because of far-reaching programs in the public and parochial schools. Some 48,000,000 children have had one or more injections, but 15,000,000 have still had none.

In contrast, adults from 20 through 39 years of age show a poor record. Only 16,000,000 have had one or more injections, while 30,000,000 still remain completely unvaccinated.

It is yet too early to draw scientific conclusions in regard to a drop in polio cases. While the widespread use of the Salk vaccine has been an important factor, scientists point out that 1957 may have been a year of low polio virulence.

In the first 11 months of 1957, only 5747 polio cases were reported in the entire nation. This is a decline of 62% from the corresponding 1956 figure of 14,974 and a drop of 83% from the 1952-1956 five-year average of 34,321 cases for the first 11-month period.

In specific areas of the country the drop in polio cases was even more spectacular. Chicago, for instance, reported only 18 cases in the first 11 months of 1957, as compared with 1105 cases in the first 11 months of the epidemic year of 1956, a drop of 98%.

Massachusetts reported only 24 cases for the first 11 months of 1957, as against a 1952-1956 five-year average for the same period of 1227 cases, a drop of 98%.

Minnesota reported only 52 cases, as compared with a 1952-1956 average of 1539, a decline of 97%. All of New England reported only 81 cases, as compared with the 1952-1956 average of 2127, a decline of 96%.

The smallest regional decline from the five-year average was 71%, in the west south central states of Arkansas, Louisiana, Oklahoma, and Texas, with 1077 cases in the first 11 months of 1957, as compared with 3735 for the same period in the years 1952-1956.

The National Foundation used $21,700,000 in 1957 to bring medical care and rehabilitation to 57,800 polio patients. Of this number, 53,000, or 90% of the total, were patients stricken in previous years. In 1958 the National Foundation estimates it will need $21,100,000 for patient aid.

"Thus we see that while 'new' cases continue to drop, 'old' cases still require millions of dollars," Mr. Basil O'Connor said. "Since its founding in 1938, the National Foundation has used a total of $279,400,000 to bring medical care and rehabilitation to 325,000 polio patients."

A massive nationwide survey of polio sufferers, begun last August by the National Foundation's 3100 chapters, has disclosed many patients whose cases never were officially reported. The National Foundation now hopes, under its 1958 March of Dimes campaign theme, "Survival Is Not Enough," to bring to many of them the fruits of modern rehabilitative science.

Research and Professional Education.—Two other important National Foundation programs, energetically pursued in 1957, will be expanded in 1958. To its scientific research program will be alloted $4,700,000 in the new year. Part of this sum will be used by Dr. Jonas E. Salk and his University of Pittsburgh associates to continue basic investigations on monkey heart cells grown in laboratory cultures, which may have a bearing on cancer research.

An additional $4,000,000 will be alloted in 1958 to professional and public education. This includes the National Foundation's program to finance the training of sorely needed doctors, scientists, physical therapists, medical social workers, and other experts.

Books

BOOKS RECEIVED

Management of the Handicapped Child. Edited by H. Michal-Smith. Price, $6.50. Pp. 276. Grune & Stratton, Inc., 381 Fourth Ave., New York, 1957.

Aids to the Diagnosis and Treatment of Diseases of Children. By F. M. B. Allen. Tenth edition. Price, $3.00. Pp. 302. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2.

Bone Diseases in Medical Practice. By I. Snapper. Price, not given. Pp. 229, with 47 illustrations. Grune & Stratton, Inc., 381 Fourth Ave., New York, 1957.

No and Yes on the Genesis of Human Communication. By Rene A. Spitz. Price, $4.00. Pp. 170. International Universities Press, 227 W. 13th St., New York 11, 1957.

Practical Notes on Nursing Procedures. By Jessie D. Britten. Price, $4.00. Pp. 192, with illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1957.

Microscopic Anatomy of the Temporal Bone. By Wolff, Bellucci, and Eggston. Price, $12.50. Pp. 414, with illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore, 1957.

The Normal Child. By R. S. Illingworth. Price, $7.00. Pp. 357, with illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1957.

BOOK REVIEWS

Congenital Anomalies of the Viscera. By J. L. Bremer. Price, not given. Pp. 202. Harvard University Press, Cambridge 38, 1957.

This textbook of applied human embryology is intended for the medical graduate who wishes to broaden his understanding of congenital abnormalities.

The material is discussed by organ systems. Abnormalities of the central nervous system, the skin, and the extremities are not included. Each chapter is introduced by a brief concise resumé of normal embryological development. There follows a more lengthy discussion of various anomalies arising from disturbances in normal development. A greater number of illustrations would enhance this portion of the text.

The descriptive nature of the book has largely precluded the use of a large body of interesting experimental embryology. The practical applications of fetal endocrinology to the development of the genitalia have not been discussed. Pediatricians will probably be disappointed by the absence of discussion concerning the syndrome of agensis of the abdominal musculature, as well as the syndromes of renal agenesis associated with the formative years and the Bonnevie-Ullrich syndrome with gonadal dysgenesis.

THOMAS H. SHEPARD, M.D.

The American Fluoridation Experiment. By F. B. Exner and G. L. Waldbott. Price, not given. Pp. 277. The Devin-Adair Company, New York, 1957.

The spirit in which this book is written is set in Rorty's introduction: "It [the fluoridation program] is the first time that public-health officials have deliberately falsified, distorted, and suppressed scientific information tending to impugn the safety of a public-health measure."

The animosity of the authors toward the United States Public Health Service is further evidenced by Exner's remark: "There is, in fact, every evidence that the primary purpose of fluoridation is not directed against dental decay; and that the real desire is for a legal precedent for compulsory medication in noncommunicable disease." These are harsh statements, for which I find no satisfying evidence.

Two aspects of the book will be discussed here: 1. Does water fluoridated at about one part per million reduce dental caries? 2. Will such water produce harmful effects on the human body?

As to reduction caries, Exner writes that the DMF ratio (the number of decayed, missing, and filled teeth per one hundred persons) is of no value and that therefore the beneficial results of fluoridation demonstrated by this method are valueless. Throughout the world, the DMF ratio is accepted as a very useful method of determining rates of dental decay. Exner writes that "The fallacy of the DMF rate is avoided by using incidence rate" based on the percentage of people free from caries, but he fails to say that by means of the incidence rate increased freedom from caries was demonstrated. Exner further writes: "Meanwhile, Blayney, at Evanston, Illinois, was trying to run an honest and scientifically respectable experiment . . . He was excoriated unmercifully at the Fourth Annual Conference in 1951, for being too honest. Since then we have heard nothing about there even being an experiment at Evanston."

Actually, from 1951 to 1956 Blayney published four papers which showed the same reduction in dental caries as had been observed in the ten-year studies.

Second, as to harmful results of fluoridation, the objection to fluoridation on the basis of engineering difficulties was answered in a recent panel discussion of leading water engineers. It was concluded that, with a known rate of flow at some point, fluoride can be added in the exact amount desired and that it will extend to the extremities of the system without measurable lessening or abnormal concentration.

Exner writes: ". . . the Public Health Service, if water is fluoridated, expects some 15 to 20 percent of children to have their teeth permanently disfigured by fluoride, while another large percent will fail to obtain any *benefit*." No author is cited or reference given for this statement, which is a direct contradiction of what the United States Public Health Service contends—that disfiguring fluorosis will not be produced when water contains one part of fluoride per million.

Dr. Exner states that the discolored dental fluorosis of two patients was the result of drinking well water during childhood "containing considerably less than one part per million of fluoride." This matter has been investigated. The results show that, in point of fact, water from one well never had been examined and that water from the other contained 2.1 parts of fluoride per 1,000,000 thus nullifying Exner's statement.

Having described his concept of the syndrome of fluoride poisoning, Waldbott writes, "So far, the evidence that this is fluoride poisoning is not final." The facts on which the assumption of poisoning is based are not pertinent. When 5.6 gm. of sodium fluoride was administered intravenously in nine days without the production of signs or symptoms, then 1.6 gm. administered by mouth over a period of two years cannot be held responsible for a multiple-symptom syndrome of poisoning. This is in agreement with the opinion of Dr. Hornung, a German physician and health officer, after a personal interview with Waldbott and study of his syndrome.

Dr. Waldbott writes: "Two fatalities from drinking natural-fluoride water are reported: one by Linsman and McMurray of a twenty-two-year-old soldier with a cystic kidney who had lived for seventeen years in areas where the water contained fluorides varying in concentration from 1.2 to 5.7 parts per million. The description of this fatality strongly indicates that its cause was not the kidney disease, but general cachexia as described by Roholm in chronic industrial fluorosis."

The facts in this case are that a soldier gained twenty-three pounds during his year in the Army and did not have either cystic kidneys or fatal cachexia, but, rather, badly damaged kidneys resulting from obstruction caused by a cord bladder. He actually died of acute terminal pyonephrosis.

In the second case the patient actually had exstrophy of the bladder resulting in enormous bilateral hydronephrosis. She died from renal failure and not from "drinking water containing fluoride at about two parts per million 'and above'," as Waldbott claims.

The very complete report of the New Zealand Commission on Fluoridation drew the following conclusions from the publications of Waldbott and Exner, on which the book under review is based.

"345. We are satisfied that there is no causal relationship between any of these signs and symptoms [of the Spira-Waldbott syndrome] and the ingestion of water containing 1 ppm of fluoride and food cooked in this water.

"97. We consider the [Exner] report as a whole to be lacking in objectivity, that it frequently fails to represent the real opinion of quoted authorities and that it is the work of a skillful propagandist."

This book cannot be recommended.

HENRY F. HELMHOLZ, M.D.

The Fight for Fluoridation. By Donald R. McNeil. Price, not given. Pp. 241. Oxford University Press, New York, 1957.

In his book, "The Fight for Fluoridation," Donald R. McNeil recounts the entire story of fluoridation for the prevention of dental decay, from the early years in which the objective was to prevent "Colorado stain" ("Texas teeth," mottled enamel) through those in which it was recognized that mottled enamel is associated with resistance to dental decay (even before we knew what caused mottling). He continues to the era in which it was learned that it is possible to achieve partial immunity to dental decay without mottling. Finally, he describes the process of learning from nature's fluoride experiments how to adjust the fluoride content of water to the level of about 1 ppm, a concentration which will reduce the rate of dental caries but which will not induce disfiguring fluorosis of the teeth or other harmful effects in the human being.

McNeil has gathered together an immense amount of material: letters, pamphlets, articles, and clippings from both the proponents and the opponents of fluoridation. These data have been deposited with the State Historical Society of Wisconsin for future reference. A critical analysis of the scientific material is hardly to be expected in a book of this kind. The author does provide a picture of the setting and various cooperating groups in the campaigns which resulted in defeat of fluoridation programs in Stevens Point, Wis., and Seattle, Wash., with considerably less detail of the successful referenda in San Francisco and Milwaukee.

As has been true of many other public-health measures, the fluoridation of public water supplies attracted its share of opposition from those against change. As the author shows, the opposition ranged from a small group of dentists and physicians who felt "that America was rushing too fast into a public health experiment" to the extremist group that considered fluoridation a "Communist plot" or "a Jewish plot to conquer the world" or "chemical rape." In between were the political allies consisting of "chiropractors," "Christian Scientists," "the health food advocates," "the naturopaths," and other persons or organizations, such as the "Citizens Medical Reference Bureau," the chief target of which previously had been vaccination.

As related by McNeil, from 1945 until 1951 a small group of Wisconsin dentists headed by Dr. John G. Frisch constantly worked in favor of the fluoridation of public water supplies as a general public-health measure. Their efforts were so effective that in 1950 in Wisconsin there were three times as many localities with fluoridated water as in the other forty-seven states. During this same period the United States Public Health Service and the American Dental Association in no uncertain terms insisted upon waiting until the results of the pilot studies were at hand before approval of fluoridation as a mass procedure should be forthcoming.

Possibly as a result of the early conservative attitude of some outstanding physicians and dentists who asked that approval of fluoridation be delayed "until the studies are completed," and of the extremists' unwarranted charges of poisoning and violation of individual rights brought about by fluoridation, the progress of fluoridation of public water supplies was slower than had been hoped for. This was true even after approval by the United States Public Health Service, the American Dental Association, and the American Medical Association. The opponents used the following dual approach: "They challenged on scientific grounds the merits of fluoridation and condemned the measure as a violation of individual rights leading to an encroachment of the power of the state on the lives of citizens." McNeil writes further: "The wide-ranging arguments which opponents drummed into the ears of the citizenry often gave a ring of authenticity to their charges, and many citizens believed them."

The completion in 1955 of the ten-year studies in Grand Rapids, Newburgh, and Brantford brought definite evidence of reduction in dental caries as a result of fluoridation of water and absence of any fluorotic discoloration as the first sign of an untoward effect of fluoridation. The author in his final paragraph sums up as follows. "The anti-fluoridation 'crusade' was a political protest movement against the scientific organizations and a government which

heeded their wishes. Fluoridation became a battle over who should decide the issue, the people, or their democratically elected officials, acting on the advice of scientific experts."

HENRY F. HELMHOLZ, M.D.

Expectant Motherhood. By Nicholson J. Eastman. Third edition, revised. Price, $1.75. Pp. 198, with 13 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1957.

From the opening chapter, "Signs and Symptoms of Pregnancy," to the final one, "The Newborn Baby," the third edition of "Expectant Motherhood" is the most complete book of its kind that I have read. To the large number of prospective mothers whose understanding of the biology of conception and the processes of childbirth needs strengthening, this book can be highly recommended. This book also answers fully most of the questions regarding diet, hygiene, and discomforts of pregnancy that might be asked. The busy practitioner, generalist, or obstetrician, therefore, can save much valuable time by referring to this easily-read book, so well directed, to the lay person.

SOLOMON C. WERCH.

Orthopedic Surgery in Infancy and Childhood. By Albert B. Ferguson Jr. Price, $15.00. Pp. 508, with 504 illustrations. The Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1957.

Dr. Ferguson's book admirably fills a void which has existed in orthopedic teaching. Now with this work and Dr. Blount's volume, "Fractures in Children," good texts are available for both the pediatrician and the orthopedic surgeon, and the field of orthopedic surgery in children is adequately covered. Dr. Ferguson states in the preface that he has omitted consideration of fractures because of the excellence of the other text.

Well-written and well-organized, "Orthopedic Surgery in Infancy and Childhood" presents topographically in its first six chapters the important congenital and acquired deformities and conditions seen by the orthopedic surgeon. In the last four chapters Dr. Ferguson discusses the conditions affecting special organ systems, namely, bone, muscle, nerves, and finally, tumors of bone. In each category he gives brief but adequate accounts of the etiology, clinical findings, pathology, and treatment. Of necessity he has limited his discussion to essentials, and wisely he has not made any attempt to present various operative techniques in detail.

This book should be a valuable text for pediatricians and for residents in orthopedic surgery. Since children's orthopedic surgery is a recognized special branch of the general field, such a book as this logically is needed, and Dr. Ferguson has accomplished his mission in a most satisfactory manner.

EDWARD D. HENDERSON, M.D.

Adrenal Function in Infants and Children: A Symposium. By Lytt I. Gardner. Price, not given. Pp. 221. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1956.

The purpose of this concise treatise was to bring together as much information as possible on the subject matter, so that those attending the conference would be fully informed of research under way in the field and might profit from the comments and criticisms of their colleagues and peers.

The book itself is nicely published on good paper with fine quality of photographs and tables. It is a credit to the editor that so much material could be compiled in so few pages that bear upon a topic which is undergoing rapid change at the present time.

In my opinion this is a very complete synopsis, that forms a good background from which clinicians and investigators may draw valuable aid in the present and future. The material compiled in this book forms a staging point for the next steps in this field, namely, elucidation of enzymatic mechanisms involved and further details of the nature of congenital and functional disorders.

Although the book contains a good section dealing with adrenal function in rheumatic fever, there is very little material on the subject of adrenal response to other types of inflammatory processes or specific infections. There is a good section dealing with the effects of androgens on growth. This book is a valuable addition to the library of pediatricians and those physicians whose practice requires special knowledge in the field of endocrinology as it applies to childhood.

ROBERT A. ALDRICH, M.D.

The Early Detection and Prevention of Disease. Edited by John P. Hubbard. Price, $7.50. Pp. 350. McGraw-Hill Book Company, Inc., 330 West 42d St., New York 36, 1957.

This very readable and stimulating book is the result of a five-day symposium undertaken by the American College of Physicians and is devoted entirely to the topic represented by the title of the book. The editor is to be commended for his slection of material; each chapter is written by one of the twenty-eight clinicians who participated, and, therefore, a variety of interests are represented.

The pediatrician should take a special pride as he reads this book in the realization that the clinical practice of pediatrics has, unlike most other specialties, "crossed the half-way mark in its trend" toward preventive medicine, through the care of well persons. The excellent chapter entitled "The Demand for the Clinical Practice of Preventive Medicine" provides ample evidence that the public is aware of the necessity for preventive medicine and that when it is presented properly they will take advantage of it. It is also pointed out that formal medical education has fallen far short of preparing the graduating physician to contribute much toward the education of his patients in the concepts of preventive care.

It is the stated purpose of the symposium to suggest a formula or technique which the practicing physician might use to determine whether his patients are functioning normally and are not heading for trouble. Several of the authors concluded that present day knowledge in their special field of interest does not allow for adequate preventive measures. Others, rather frankly, admit that prevention of disease in their field had not been very prominent in their thoughts until the challenge of preparation for this symposium was presented to them.

Most of the chapters in the book subscribe very nicely to the avowed purpose of the symposium and will be of value to the practicing physician in internal medicine or general practice. In the field of mental health and the early detection of deviations from normal, the discussion of the adult woman is particularly well presented. While immunization procedures, both active and passive, have been prominently considered in the field of preventive medicine, it is unfortunate that the chapter on this topic falls short of being a useful guide to the practicing physician. The author confines himself to a review of the diseases against which immunization may be carried out.

This is an excellent book, both readable and stimulating, for the practicing physician and student of medicine. It presents an excellent review of current knowledge concerning the measurement, maintenance, and improvement of health as well as the early detection of disease states and applicable preventive measures.

HENRY B. BRUYN

Child Behavior. By Frances L. Ilg, M.D., and Louise Bates Ames, Ph.D. Price, $3.95. Pp. 364. Harper & Brothers, 49 E. 33d St., New York 16, 1955.

This is a volume in which a discussion of child behavior is presented primarily for the use of parents and which is available in most bookstores. The book is divided into two parts; the first, a presentation of the usual pattern of development of children, followed by a discussion of some of the variations which occur. In the second part there is a more detailed discussion of behavioral patterns and the difficulties that arise in relation to development. Throughout there is great emphasis on the dynamic aspects of behavior and the fact that many problems will be solved when the child passes to the next "age and stage"; perhaps its chief message to the concerned parent, then, is one of advising patients to wait for time to take care of the situation. In addition to this message there are, however, many helpful suggestions for the problems of behavior that ordinarily arise. If books can help parents in the solutions to these problems, then this one should be adequate.

Ultramicro Methods for Clinical Laboratories. By Edwin M. Knights, Roderick P. MacDonald, and Jaan Ploompuu. Price, $4.75. Pp. 128, with 18 illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1957.

The authors have produced a handy little manual for use in a hospital ultramicrochemistry laboratory. They emphasize the usefulness of such a laboratory, the necessity for its separation from the "frenzied activity of the routine hospital chemistry department," and the requirement for special training and techniques. The first three chapters, twenty pages, include a section in which the special equipment required is described and, in some cases, pictured.

The equipment considered necessary to operate the basic hospital microchemistry laboratory is listed and described. Also included are notes on the technique of using ultramicro pipettes, obtaining capillary blood, and separating the serum for analysis.

The next eighteen chapters, one hundred three pages, describe the selected procedures for a number of tests, most of which are performed upon 10- to 30-microliter specimens of serum and utilize micromodifications of rather well-known methods. Sodium and potassium are determined by flame photometry, with use of the Baird instrument. Other chemical determinations described and the methods modified for their use include calcium (Rehell's EDTA method), chloride (Shales and Shales), inorganic phosphorus (Benedict and Theis), glucose (Somogyi), phosphatase (King and Armstrong), bilirubin (Malloy and Evelyn), and CO_2 combining power by use of the Kopp-Natelson microgasometer. Also included are sections on serum protein, albumin, urea, cholesterol, icterus index, thymol turbidity, cephalin flocculation, C-reactive protein, paper electrophoresis, microflocculation tests for syphilis, and microhematocrit determinations.

The authors have attempted to fill the need for a practical manual of methods for use in hospital ultramicrochemistry laboratories. They have produced a simple manual which will tend to reassure those who have been fearful of adventuring into the intricacies of ultramicro chemistry. On the other hand, one wonders whether it might not have been wiser to emphasize some of the difficulties, to point out some of the likely sources of error, and to suggest methods of minimizing them. Exact information is given regarding the reproducibility of some methods, but the phosphorus method is said to give results which "are in agreement with the Karr urease method," and the cholesterol method "will give values which agree with the Bloor method up to 400 mg. per cent." More discussion of these problems would have been preferable to the approximately eleven pages on the interpretation of the results—a discussion which might better have been left to textbooks of clinical pathology.

LESTER D. ELLERBROOK, Ph.D.
ROBERT A. ALDRICH, M.D.

Perinatal Loss in Modern Obstetrics. By Robert E. L. Nesbitt Jr. Price, $12.50. Pp. 432, with 108 illustrations, including 10 in color. F. A. Davis Company, 1914-1916 Cherry St., Philadelphia 3, 1957.

The author has written much on the subject of perinatal morbidity and mortality. This is a very complete helpful book and stresses the interdisciplinary approach to the problem. It emphasizes the importance of perinatal or neonatal mortality conferences involving obstetricians, pediatricians, pathologists, and others concerned.

This book is divided into fourteen chapters which survey the causes of perinatal wastage, and it beautifully illustrates the interdisciplinary approach.

For all persons concerned with perinatal problems, there is a wealth of statistical data and excellent bibliographies on most subjects. The particular experiences quoted are from the Johns Hopkins obstetrical service, and an appendix gives the perinatal mortality code sheet of Johns Hopkins Hospital.

From the pediatrician's point of view, there is a bird's-eye survey and bibliography of such subjects as prematurity, infections, and hemolytic diseases, with the stress on the interdisciplinary approach.

This book would be a very valuable addition to the shelves of nurseries for newborn infants and would provide considerable information and ideas which could be utilized in hospital perinatal mortality conferences.

ROBERT B. LAWSON

Comparative Aspects of Haemolytic Disease of the Newborn. By G. Fulton Roberts, M.A., M.D., Fellow of Jesus College, Cambridge. Price, $3.00. Pp. 199. William Heinemann, Ltd., 99 Great Russell St., London, W. C. 1; Grune & Stratton, Inc., 381 4th Ave., New York 16, 1957.

An excellent book. Although the 148 pages of text are packed with facts, the author has managed to follow his whim "to express the material in the form of continuous prose without the aid of diagrams and figures." His prose makes fine reading.

The important groundwork which must be mastered to understand hemolytic disease is well and adequately set forth. The author threads his way skillfully through the various theories

relating to the formation and nature of antibodies, to the genetics of the antigens, to kernicterus and in fact to all aspects of the problem, including treatment.

Of great interest is the summary of old medical writings, going back to 1609, when Louyse Bourgeois, midwife to Marie de Medici, wrote of the delivery of twins. One was stillborn and hydropic, while the other lived for a while and was jaundiced. Although through the years there are many references to all the clinical manifestations of Rh disease, including a description of a kernicteric brain by Wrisberg in 1764, a common cause for hydrops, jaundice, and anemia was not clearly stated until the papers of Ferguson in 1931 and Diamond, Blackfan, and Baty in 1938.

Separate chapters are devoted to hemolytic disease as it occurs in the horse and in the pig, and a third chapter describes the experimental production of hemolytic disease in the guinea pig, rat, dog, and rabbit. Somewhat to my surprise, Roberts does not comment on the possible significance of two features of the animal disease in relation to each other, namely, the absence of significant levels of bilirubin in the blood and the failure of kernicterus to develop.

This book is recommended to any doctor or biologist, and it should be considered obligatory reading by those who wish to know all about hemolytic disease of newborn animals and man.

RICHARD L. DAY

An Atlas of Cardiac Surgery. By Jorge A. Rodriguez. Price, $18.00. Pp. 250, with numerous illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1957.

The book "An Atlas of Cardiac Surgery" prepared by Jorge A. Rodriguez, M.D., is a most lucid outline of current cardiac surgical techniques presented in atlas form. In the preface the author acknowledges that it might seem unwise to attempt to compile an atlas of standard procedures in cardiac surgery in view of the rapidly changing techniques. Nevertheless, it was the author's conviction that a compilation of current established procedures would be of value to all physicians, regardless of their particular field. In this, the author has admirably succeeded.

The book is divided into six basic sections. The first section of the book, dealing with surgical anatomy of the heart and great vessels, is particularly valuable because the drawings are based upon the author's own dissections. The illustrations are unusual in that their orientation is not purely anatomical but surgical. Thus, many views will be familiar to thoracic and cardiovascular surgeons but will be quite new to those who do not have the opportunity to view the heart and great vessels in the operating room.

The second section, entitled "Adjuvants to Cardiac Surgery," effectively summarizes recent advances in anesthesia, hypothermia, and extracorporeal devices for open and closed cardiac surgery. Once again, the author combines his own line drawings with articulate sidenotes.

The remaining sections of the book are concerned with the surgical management of the commoner congenital and acquired cardiovascular lesions. In preparation of this portion of the atlas, the author visited various centers throughout the country, made sketches in the operating room, and discussed the various features of each surgeon's technique with him in detail. On the basis of these sketches and discussions, twenty-nine procedures were included in the atlas.

The book is highly recommended to all physicians who are either directly or indirectly involved in the field of cardiovascular surgery.

ROBERT S. LITWAK, M.D.

Annual Review of Medicine: Vol. 8. Edited by David A. Rystand and William Creger. Price, $7.00. Pp. 530. Annual Reviews, Inc., Grant Ave., Palo Alto, Calif., 1957.

These reviews are published annually under the general editorship of Dr. David Rytand, Professor of Medicine at Stanford, with the pediatric point of view represented on the Editorial Committee by Dr. Rustin MacIntosh. Certain subjects are selected, and the outstanding persons in the field are asked to review them. For each particular subject, the reviewer does a general survey of the recent literature, with a thumbnail sketch of the reported findings and significant conclusions, and includes a really excellent bibliography.

The last chapter of the book is devoted to pediatrics, under the editorship of Dr. F. Howell Wright, of Chicago, who takes up the subjects of poliomyelitis, newborn infants, and endocrine

disorders, among a few other things which were of particular interest to him. The chapter on pediatrics, however, is by no means the only one of considerable interest to pediatricians; many chapters stand out: The chapter on adrenocortical hormones in the management of infection, by Drs. E. H. Kass and M. Finland is as applicable to pediatrics as it is to internal medicine; there is a chapter on infectious diseases, particularly on biological and chemical means of prophylaxis; there are two good chapters on the cardiovascular system—the medical aspects written by Dr. C. G. Parsons, of Birmingham England, and the surgical aspects reported by Dr. Lillihei, from Minnesota; there is one on radioactive isotopes in medicine; there is one on connective tissue diseases, and there is one on exprimental retrolental fibroplasia by Dr. N. Ashton, which is an excellent review of the recent work in the field of the relation of oxygen to the mechanism of production of fibroplasia.

These reviews would be of help to anyone who might be preparing a paper, talk, or rounds, who is not so familiar with the particular field as to know all the outstanding contributions. This volume is for those who are interested in the broader field of medicine as well as for pediatric departments, pediatric libraries, and children's hospitals. It is an excellent source of thumbnail reporting with a good bibliography on many subjects of pediatric interest.

ROBERT B. LAWSON

The Story of Peptic Ulcer. By Richard D. Tonkin. Price, not given. Pp. 71, with numerous illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia, 1957.

In this small volume, Dr. Tonkin holds the reader's interest by keeping him amused while presenting the essentials of what is known about peptic ulcer. The light breezy style of the text, together with the many cartoon-type illustrations, sets the stage for transmitting the author's ulcer prescription, which calls for large quantities of common sense well mixed in a vehicle of philosophy.

The factors usually considered in the etiology of peptic ulcer are presented with a broad-minded point of view. The reader is left with the proper impression that numerous facts regarding this disease have accumulated and yet we do not have sufficient information to tie all the facts into a universally accepted etiological mechanism.

In my opinion, the majority of our leaders in the field of gastroenterology will take no major exception to the program of management presented in this book as regards uncomplicated duodenal ulcer. However, it is generally accepted that the management of gastric ulcer presents specific problems which are not touched upon in this volume. Admittedly, it would be difficult to go into the problem of differentiating gastric ulcer from gastric malignancy in a book designed for patient reading, and this material is undoubtedly rightfully omitted for this reason.

The book has a real potential as a therapeutic agent in the treatment of ulcer if used discretely by the patient's physician. It certainly cannot take the place of expert counseling and explanation on the part of the doctor. However, with proper selection of patients and preliminary discussion of the ulcer problem between physician and patient, the reading of this book should help many an ulcer victim gain the philosophy toward his lesion which the author hopes he can achieve.

WINSTON K. SHOREY

Handbook of Speech Pathology. Edited by Lee Edward Travis. Price, $12.00. Pp. 1088, with numerous illustrations. Appleton-Century-Crofts, Inc., 35 W. 32d St., New York 1, 1957.

Lee Edward Travis, who has edited as well as contributed to this volume, indicates that this work would not have been possible from the pen of one man; therefore, twenty-seven authorities in the various areas of speech pathology have contributed its thirty-three chapters.

In the preface, Dr. Travis reminds the reader that a speech disorder is a disorder of the person as well as a disorder in the reception and transmission of spoken language. This premise is reflected in the make-up of the book.

The book is divided into four parts. Part I, "Basic Considerations in Speech Pathology," includes discussions of development of speech and incidence of speech disorders, of neuro-physiology and acoustics of speech, of necessary instrumentation, and of terminology, as well as methods employed for diagnosis of speech disorders. The glossary of terms frequently used in speech pathology is found in the chapter on terminology and nomenclature.

Part II deals with those speech disorders associated with organic abnormalities, these being deafness, aphasia, mental retardation, cerebral palsy, cleft lip and cleft palate, dental abnormalities, and so on. Part III is concerned with speech and voice disorders unrelated to organic abnormalities, such as functional disorders of articulation and of voice, and stuttering. In each chapter, it was necessary for the writer to condense a tremendous amount of material. Three of the authors discuss the relationship of psychotherapy and speech therapy in Part IV.

There is less unevenness in writing from chapter to chapter than one would expect from this number of writers. Presumably because of the material to be covered, some chapters require more background knowledge on the part of the reader. One is aided, however, in those chapters dealing with technical aspects by numerous illustrations and graphs. The bibliographies at the end of each chapter are indeed comprehensive.

In my opinion, the book is adapted primarily to the student of speech pathology. This is not a book for a physician to hand to a patient to read; however, in view of its wealth of material, it could well serve as a reference book for a physician needing reliable information on this subject.

JOSEPHINE SIMONSON.

The Rehabilitation of Speech. By Robert West, Merle Ansberry, and Anna Carr. Third edition. Price, $7.50. Pp. 676, with 53 illustrations. Harper & Brothers, 49 E. 33d St., New York 16, 1957.

Changes in the field of speech correction as a result of increasing interest and constant research explain the necessity for a third edition of this well-respected textbook in speech pathology (first edition, 1937).

In Book One, Dr. West discusses the pathology of speech and the rationale of its rehabilitation. His first two chapters, "The Neurophysiological Mechanism for Speech Production" and "The Normal vs. the Abnormal" lay the necessary foundation of ideas, facts, and principles for understanding succeeding chapters. He then devotes a chapter to critical examination of each of the following problems: dysphonia, dysarthrias, aphasia, dyslalias, the deaf and the hard-of-hearing, stuttering, secondary disorders of speech, and Mongolism.

Book Two, titled "Remedial Principles," was written by Merle Ansberry and Anna Carr. Here techniques of rehabilitation for the various defects of speech are discussed in detail, with many suggestions for specific exercises.

The fifty-five page glossary near the end of the book is a scientific comprehensive collection of terms. If a more complete discussion of a word is given in the text, the reader is so informed and only a short definition appears in the glossary. Pronunciations of words in the glossary are indicated by phonetic symbols, which may be slightly confusing to those readers not familiar with the system used by the International Phonetic Association.

The physician will find most helpful the easily accessible information in the appendixes: (1) Code of Ethics of the American Speech and Hearing Association, (2) Clinical Certification Requirements of the American Speech and Hearing Association, (3) Minimum Requirements for Hearing Programs Offering Guidance in Selection of Hearing Aids, (4) Tests of Hearing, and (5) Tests of Articulation. Furthermore, information on incidence of speech disorders and on classification of speech disorders is quickly available in the introduction.

It is my opinion that this book would be a good reference book in speech pathology for the physician.

JOSEPHINE SIMONSON.

Doctor, your dietary decision can build Blue Ribbon babies

The baby who wins the blue ribbon is the one whose doctor—no one else—determines its exact nutritional needs.

GET YOUR BABIES OFF TO A STRONG START WITH...

Varamel®

A scientifically formulated evaporated milk product prepared exclusively from Grade A Milk

Happy Lynn Patricia, aglow with health, is a Blue Ribbon winner, pride of her doctor who selected VARAMEL to get her off to a strong start.

VARAMEL BUILDS BLUE RIBBON BABIES

- Made from milk of outstanding purity.
- Scientifically formulated for optimum nutrition.
- Helps prevent colic.[1] Butterfat replaced by easily digested vegetable oils.
- Twice homogenized for better digestion and absorption.
- Permits prescribing carbohydrate of choice. No sugar added.
- Provides adequate amounts of all known essential vitamins plus much-needed iron.
- Helps doctor control infant feeding longer. Advertised to the medical profession only. Available in drug stores.
- Economical to use— eliminates need for additional vitamins and iron.

Other products–Baker's Modified Milk—a completely prepared formula in liquid and powder form.

Approximate Analysis

Protein	4.9%	Calcium	0.19%
Carbohydrate	8.3	Phosphorus	0.15
Fat	5.8	Iron	0.0016
Ash	1.2	Moisture	79.8

22 Calories per fl. oz.

Average dilution—equal parts of Varamel and water plus sufficient carbohydrate to make 20 calories per fluid ounce.

1. Breslow, L.: Clinical Approach to Infantile Colic. J. Pediat. 50: 190-206, 1957. (Reprint sent on request.)

FURNISHED GRATIS TO HOSPITALS FOR NURSERY USE

The Baker Laboratories, Inc. • Cleveland 3, Ohio

Milk Products Exclusively for the Medical Profession

For

CONSTIPATED BABIES AND CHILDREN

laxative modifier of milk—
promotes aciduric intestinal flora

Malt Soup Extract promotes growth of favorable aciduric intestinal flora and provides mild peristaltic stimulation. Safe, effective, non-habit forming—as confirmed by medical literature and clinical use for over 45 years.

FOR INFANTS: A gentle laxative modifier of milk. Just add one or two tablespoonfuls routinely to the day's formula, or in water for breast-fed infants. Prompt results, even in stubborn cases.

FOR CHILDREN: One or two tablespoonfuls with breakfast and at bedtime, by spoon or in milk. Makes a delicious "malted" drink.

NOW 2 FORMS

* Specially processed non-diastatic barley malt extract neutralized with potassium carbonate.

LIQUID:
In 8 oz. and Pt. jars.

POWDER:
In 8 oz. and 16 oz. jars.
(use heaping measure)

SEND FOR SAMPLES

POWDER

LIQUID

BORCHERDT CO. 217 N. WOLCOTT AVE. CHICAGO 12, ILL.

MALT SOUP EXTRACT

HEART DISEASE

an indiscriminate killer, touching the young or old

The "well-informed" patient can help you, by helping himself. For reliable information on this subject, have your patients read:

HEALTHY HEARTS

A collection of Hygeia articles: The War Against Heart Diseases Still Rages, Hearts in the Breaking, Preventing Heart Attacks, Heart Diseases of Middle Life.
20 pages, 20 cents

STROKE

In relation to overweight, hardening of the arteries, high blood pressure, blood clots, diabetes.
by William W. Bolton
8 pages, 15 cents

HEART ATTACK

Covering types of attacks, symptoms, relief and heart diseases.
by Walter Modell
12 pages, 15 cents

A KITCHEN FOR THE "TAKE-IT-EASY" COOK

Designed for the cardiac housewife, but the work-saving ideas can be applied in any kitchen. Illustrated.
by Anna May Wilson
16 pages, 20 cents

WRITE TO:

BUREAU OF HEALTH EDUCATION
AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN · CHICAGO 10

Isolation with accessibility: The infant is protected from nursery air by a spacious, transparent hood. Four iris-diaphragm ports and one hinged port provide complete accessibility.

Individually air-conditioned, the ISOLETTE® continually draws in fresh air from outside the hospital, protecting the infant from air-borne nursery pathogens, even when iris ports are open.

Positive humidity control with a simple valve. Constant, controlled recirculation of moist, fresh air maintains humidity at desired optimal level, as high as 85% to 100% —without need for additional heat.

Precise temperature control within a tolerance of 1°F., with device for cooling as well as heating, and **automatic alarm** should outside factors cause overheating.

the **Isolette**® infant incubator offers

Greater Protection for the Premature

The ISOLETTE, only "completely air-conditioned" infant incubator described and illustrated in the new 2nd edition of "*Premature Infants,*" may serve also as "an isolation unit in addition to maintaining optimal environmental conditions, and is particularly useful in caring for the smallest infants." Dunham, E. C.: *Premature Infants,* 2nd Ed., Hoeber-Harper, New York, 1955.

Moreover, "The ISOLETTE® is probably the greatest single aid available in the surgical care of the tiny infant . . . it provides well-regulated warmth and humidity and economical oxygen concentrations in a convenient working area for nurse and doctor . . . unsurpassed visibility . . . and convenience of handling . . . The isolation of the patient from his neighbors and from the contaminated or ailing doctor or nurse is an additional safeguard. Intravenous cutdowns, weighings, spinal taps and other procedures are all possible within its protective shell." Lynn, H. B.: POSTGRAD. MED., 22:493, Nov. 1957.

The Isolette®

Fresh-air-flow infant incubator by **AIR-SHIELDS, INC.**

Phone collect, OSborne 5-5200, Hatboro, Pa., and order with 30-day return privilege.
IN CANADA: AIR SHIELDS (CANADA) LTD., 8 Ripley Avenue, Toronto 3, Ont. (Roger 6-5444)

integrate your knowledge by reading these related specialty journals . . .

A. M. A. Archives of INDUSTRIAL HEALTH

A. M. A. Archives of INTERNAL MEDICINE

A. M. A. Archives of DERMATOLOGY

Designed to save you hours of reading time through visual presentations . . . to provide you with timely tips every month . . . to place useful information at your finger tips, leaving less information on your reference shelf.

Write for subscriptions to:
AMERICAN MEDICAL ASSOCIATION
535 North Dearborn Street
Chicago 10, Ill.
Dept. (PATH.)

A. M. A.
AMERICAN JOURNAL OF DISEASES OF CHILDREN

integrate your knowledge—subscribe to

A. M. A. Archives of PATHOLOGY

A. M. A. Archives of INTERNAL MEDICINE

A. M. A. Archives of OPHTHALMOLOGY

A. M. A. Archives of OTOLARYNGOLOGY

For a more complete reference shelf, we recommend these related journals. The variety of fields covered are especially appealing to the general practitioner with special interests. Each issue is important to your practice. Begin your subscriptions TODAY.

Department (D. C.)
AMERICAN MEDICAL ASSOCIATION
535 N. Dearborn St.
Chicago 10, Ill.

Begin my subscription(s) NOW, for:

A. M. A. .....

NAME .....

STREET .....

CITY .....STATE .....

New mothers sometimes think preparing an evaporated milk formula is more complicated than proprietary formulas.

Actually, since sterilization is the same, the *only* difference is that the mother adds the carbohydrate... the specific type and amount *prescribed by the physician.*

This gives the infant the advantages of his own evaporated milk *prescription* formula, readily adjustable to changing nutritional needs – a *flexibility* not possible with proprietary formulas.

The mother who knows this will not consider adding the carbohydrate any "trouble" at all!

Carnation

"FROM CONTENTED COWS"

Optimum prescription-quality in today's trend to the individualized formula.

Viokase Pancreatin 4 times the N.F. X minimum potency standards.

VIOKASE

CONFORMS TO

WHOLE PANCREAS
Not an extract!

EFFECTIVE substitution therapy in demonstrated pancreatic deficiency.

NOT ENTERIC COATED

Shwachman, H., The Child in Health and Disease, Grulee and Eley, 2nd Edit.

Shwachman, H. and Leubner, H., Advances in Pediatrics, VII, 249, 1955.

Kagan, B. M., Illinois Medical Journal, 107, 120, 1955.

Kumar, B. B., and Gibbs, G. E. A.M.A. Journal Diseases of Children, 91:606, 1956.

Literature on request.

VIOBIN, Monticello, Illinois

PRESCRIPTION SERVICE FOR

ENURESIS

NOT sold or advertised to the public. NOT available without your Rx. S. & L. ENURESIS ALARMS can be rented ONLY by patients for whom you prescribe. The alarm is used in the patient's home, under your supervision.

Professional supervision is important, but simple. A reprint from **The Journal of the A.M.A.**, describing this therapy in detail, will be enclosed with our reply to your inquiry.

Our EXCLUSIVELY PROFESSIONAL service, inaugurated in 1947, is available throughout the U. S. You need only validate our business reply order form and give it to the patient. We notify you when the patient orders an alarm, and again when it is returned.

- PROFESSIONAL QUALITY APPARATUS
- LOWEST COST, $5 PER WEEK
- CONVENIENT SERVICE
- OVER 90% EFFECTIVE
- ETHICAL

Write for Rx Forms and Brochures

S. & L. SIGNAL COMPANY, INC.
525 HOLLY AVENUE MADISON 5, WIS.

THE PEDIATRIC DEPARTMENT
of
MEMORIAL CENTER
FOR CANCER AND ALLIED DISEASES

announces that

The annual comprehensive
three day course in Pediatric Oncology
for

PEDIATRICIANS
GENERAL PRACTITIONERS
HEALTH OFFICERS

will be held

APRIL 30, MAY 1 and 2, 1958

Current developments and established methods in diagnosis, differential diagnosis and management of benign and malignant tumors, Hodgkin's disease, leukemia and reticuloendotheliose in childhood are included.

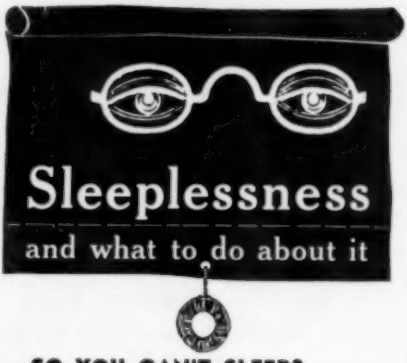
CONTENT OF COURSE: Ward rounds, Seminars, Demonstrations, Examinations of children in Pediatric, Surgical, Chemotherapy, Radiotherapy Clinics.

FACULTY: Twenty members of the Attending Staffs of Memorial Hospital and Sloan-Kettering Institute for Cancer Research.

Class limited to 15 physicians. Fee $35.00

FOR INFORMATION ADDRESS:

DIRECTOR, PEDIATRIC SERVICE
MEMORIAL CENTER
444 East 68th Street
New York, New York

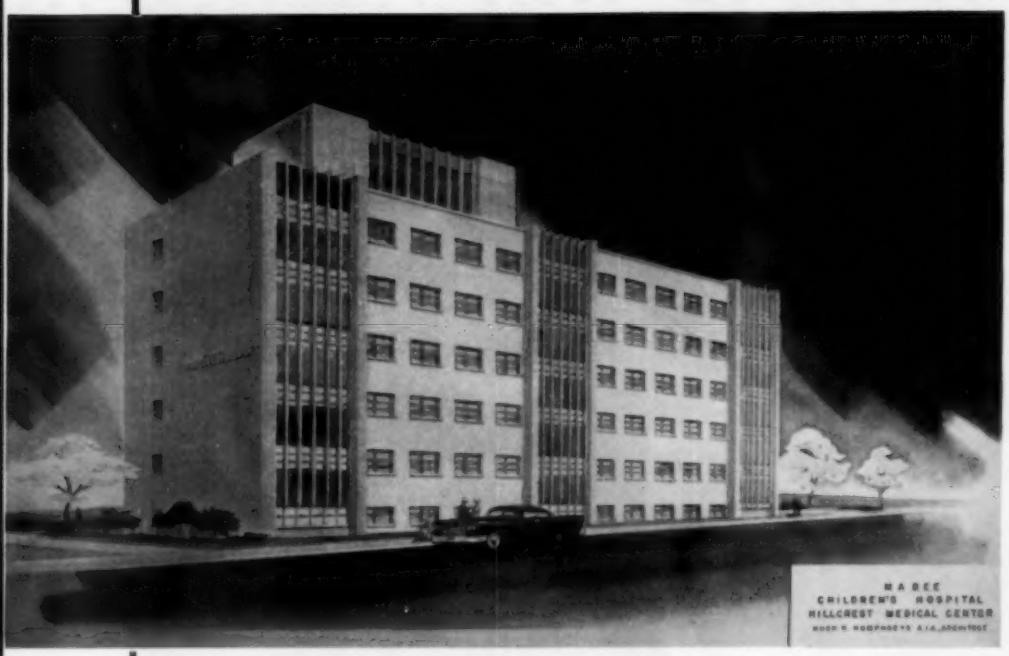


SO YOU CAN'T SLEEP?
by P. H. Fluck
8 pages, 15 cents

SLEEPLESSNESS AND WHAT TO DO ABOUT IT by Donald A. Laird, Ph.D.
8 pages, 15 cents

ROADS TO RELAXATION
by Joseph L. Fetterman, M.D.
4 pages, 10 cents

AMERICAN MEDICAL ASSOCIATION
535 N. Dearborn St., Chicago 10, Illinois



Through the benevolence of one of our philanthropists in Tulsa, Hillcrest Medical Center is building an ultra-modern, 135 bed Children's Hospital. We are also building a 200 bed addition for general patients, bringing our total bed capacity to between 700 and 800 beds.

Tulsa is one of the most modern cities in America and a good place to live.

We need some residents in pediatrics. Anyone interested please apply to the House Staff Committee at Hillcrest Medical Center, 1653 East 12th Street, Tulsa, Oklahoma.

little

How to win friends ...

The Aspirin that
Tastes So Good.

The Flavor Remains Stable
down to the last tablet.

25¢ Bottle of 48 tablets (1¼ grs. each).

We will be pleased to send samples on request.

THE BAYER COMPANY DIVISION
of Sterling Drug Inc.
1450 Broadway, New York 18, N. Y.

air
in
a
hurry

\+

protection
from asthma
for hours
with 1
convenient tablet—

Nephenalin®
PEDIATRIC

each tablet contains:		
	Aludrine (Isoproterenol HCl)	5 mg. (in coating)
	plus	
	Theophylline	100 mg. (1½ gr.)
	Ephedrine sulfate	12 mg. (3/16 gr.)
	Phenobarbital	8 mg. (1/8 gr.)

dose: Keep under tongue 5 minutes for rapid asthma relief; then swallow. Not more than 1 tablet in 4 hours, or 5 tablets per day. Bottles of 20 and 100.

Thos. Leeming & Co. Inc. New York 17, N. Y.

when sniffles hit the classroom

AND NASAL CONGESTION MAKES YOUNGSTERS MISERABLE

Neo-Synephrine®

Pediatric Nasal Spray

0.25% • 20 cc.

contains Zephiran® chloride 1:5000, antibacterial wetting agent and preservative for greater efficiency

*Designed specifically for children**

Prompt and Prolonged Decongestion Sinus Drainage and Aeration

NO STING • NO SEDATION • NO EXCITATION
In practically all patients

Plastic Unbreakable Squeeze Bottle
Leakproof, Delivers a Fine Mist

*Also well suited for adults who prefer a mild spray.

Winthrop LABORATORIES • NEW YORK 18, N. Y. • WINDSOR, ONT.

Neo-Synephrine (brand of phenylephrine) and Zephiran (brand of benzalkonium, as chloride, refined), trademarks reg. U.S. Pat. Off.